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(57) Abstract

A method of treating sexual dysfunction comprising administering a therapeutically effective amount of a combination of phentolamine and cGMP PDE inhibitor such as sildenafil, as well as pharmaceutical compositions and kits useful in those methods, are disclosed.

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COMBINATION OF PHENTOLAMINE AND CYCLIC GMP PHOSPHODIESTERASE INHIBITORS FOR THE TREATMENT OF SEXUAL DYSFUNCTION

BACKGROUND

The present invention relates to pharmaceutical compositions comprising a combination of phentolamine and cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE) inhibitors and to methods of treating sexual dysfunction, especially erectile dysfunction, comprising administering an effective amount of a combination of phentolamine and cGMP PDE inhibitors.

The use of the pharmaceutical compositions and methods of this invention results in an unexpected potentiation of human sexual response.

SUMMARY OF THE INVENTION

The present invention is directed to the use of phentolamine in combination with cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE) inhibitors for the treatment of human sexual dysfunction. Preferably, the invention contemplates the use of Type V cGMP PDE inhibitor in combination with phentolamine with sildenafil being the preferred Type V cGMP PDE inhibitor.

More particularly, the present invention relates to a method of treating sexual dysfunction, especially erectile dysfunction, comprising administering to a human in need of such treatment an effective amount of a combination of phentolamine, or a pharmaceutically acceptable salt, solvate or ester thereof, and a cGMP PDE inhibitor, or a pharmaceutically acceptable salt or solvate thereof. Preferably, the invention contemplates the use of Type V cGMP PDE inhibitor in combination with phentolamine, with sildenafil being the preferred Type V cGMP PDE inhibitor.

Phentolamine mesylate and sildenafil citrate are the most preferred active ingredients for use in the methods of this invention.

In a second aspect, the invention relates to a pharmaceutical composition comprising an effective amount of phentolamine, or a pharmaceutically acceptable salt, solvate or ester thereof, and a cGMP PDE inhibitor, or a pharmaceutically acceptable salt solvate thereof. Preferably, the pharmaceutical compositions envisioned by the present invention comprise phentolamine, or a pharmaceutically acceptable salt, solvate or ester thereof, and a Type V cGMP PDE inhibitor, or a pharmaceutically acceptable salt solvate thereof, with sildenafil being the preferred Type V cGMP PDE inhibitor. Phentolamine mesylate and sildenafil citrate are the most preferred active ingredients of the pharmaceutical compositions of this invention.

In a third aspect, the invention relates to a kit comprising in one container an effective amount of phentolamine, or a pharmaceutically acceptable salt, solvate or ester thereof in a pharmaceutically acceptable carrier, and in a separate container, an effective amount of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt, solvate thereof in a pharmaceutically acceptable carrier, with sildenafil being the preferred Type V cGMP PDE inhibitor. Phentolamine mesylate and sildenafil citrate are the most preferred active ingredients for use in the kits of this invention.

In a fourth aspect, the invention relates to a pharmaceutical composition for the treatment of human sexual dysfunction comprising a therapeutically effective amount of a first vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof, a therapeutically effective amount of a second vasodilating agent or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier. Preferably, the first vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof is an adrenergic blocker. More preferably, the adrenergic blocker is an alpha-adrenergic blocker. Also preferred is that the alpha adrenergic blocker is selected from the group consisting of an alpha1-adrenergic blocker, an alpha2-adrenergic blocker or both an alpha1-adrenergic blocker and an alpha2-adrenergic blocker. Preferably, the second vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof is a cGMP PDE inhibitor. Also preferrred is that the first vasodilating agent or a pharmaceutically acceptable salt or solvate or

ester thereof is an adrenergic blocker and the second vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof is a cGMP PDE inhibitor. The adrenergic blocker can be selected from the group consisting of phentolamine, phentolamine mesylate, phentolamine hydrochloride, phenoxybenazmine, tolazoline, dibenamine, yohimbine, terazosin, doxazosin, prazosin and the like. The cGMP PDE inhibitor can a cGMP PDE V inhibitor. Preferably, the cGMP PDE V inhibitor is selected from the group consisting of:
sildenafil,
(6R, 12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrizino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (Compound A), and
(3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (Compound B) or a pharmaceutically acceptable salt or solvate thereof.

In a fifth aspect, the invention relates to a method of treating human sexual dysfunction comprising the simultaneous or sequential administration of a therapeutically effective amount of a therapeutically effective amount of a first vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof, a therapeutically effective amount of a second vasodilating agent or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier. The classes and types of compounds which can be used in the method are described in the fourth aspect, above.

DETAILED DESCRIPTION

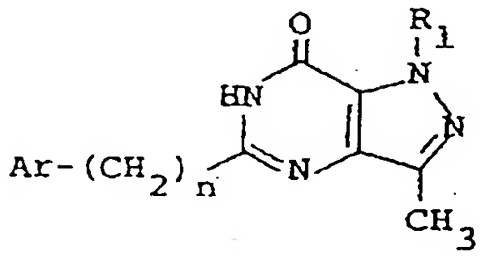
Humans include, of course, males and females. Although the pharmaceutical compositions of the present invention are envisaged primarily for the treatment of erectile dysfunction or male sexual dysfunction, they may also be useful for the treatment of female sexual dysfunction. Such female sexual dysfunction may include orgasmic dysfunction due to clitoral irregularities or disturbances.

Phentolamine, 3-[[(4,5-dihydro-1H-imidazol-2-yl)methyl](4-methylphenyl)amino]phenol, and pharmaceutically acceptable salts, solvates, hydrates, crystalline polymorph forms and the free base thereof,

are useful in the treatment of sexual dysfunction. A rapidly disintegrating tablet and method of use to treat sexual dysfunction is disclosed in United States Patent No. 5,731,339, also incorporated herein by reference. Representative formulations comprising phentolamine are disclosed in U.S. 5,731,339. Phentolamine can exist in unsolvated as well as solvated forms, including hydrated forms, e.g. hemi-hydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention. Phentolamine can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrohalic acids such as hydrochloric and hydrobromic; as well as other acids such as sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic, toluenesulfonic and other mineral and carboxylic acids known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base form for purposes of this invention. Phentolamine can also form crystalline polymorph forms or crystalline forms thereof using suitable or conventional crystallization procedures.

The present invention is directed to the use of cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE) inhibitors in combination with the salts or esters of phentolamine, preferably, with phentolamine mesylate for the treatment of human sexual dysfunction, preferably erectial dysfunction Examples of cGMP PDE inhibitors contemplated in this invention are as follows and are described in the following documents, as indicated. The disclosure of each of the below-referred to document is incorporated herein by reference.

European published application number 0201188, which discloses compounds of the formula



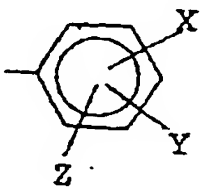
(I)

and the pharmaceutically acceptable salts thereof, in which:

R_1 is a lower alkyl of from one to six carbon atoms, a lower alkenyl of from one to six carbon atoms, a lower hydroxyalkyl of from one to six carbon atoms, a lower hydroxyalkenyl of from two to six carbon atoms, a lower aminoalkyl of from one to six carbon atoms, or a lower aminoalkenyl of from two to six carbon atoms;

n is 0 or an integer of from 1 to 4; and

Ar is a radical of the following general formula (R_2)



or 2, 3, or 4-pyridyl, in which X, Y, and Z are, independently, (1) hydrogen; (2) lower alkyl of from one to six carbon atoms; (3) halogen, (4) hydroxyl; (5) lower alkoxy of from one to six carbon atoms; - (6) nitro; (7) amino; (8) NR'R" wherein R' and R" are each, independently, (a) hydrogen or (b) lower alkyl of from one to six carbon atoms optionally substituted by (i) amino, (ii) morpholino or (iii) cycloalkyl of from, five to seven carbon atoms; (9) sulfonyl; or

(10)-$SO_2NR'R"$ wherein R' and R" are as defined above;

with the proviso that not all of X, Y, and Z can be nitro, amino, or NR'R" at once.

Preferred compounds include:

1-ethyl-3-methyl-5-phenylpyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-phenylpyrazolo[4,3-d]pyrimidine-7-one;

1,3-dimethyl-5-(4-chlorophenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(4-methylphenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(4-nitrophenyl)pyrazolo-[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(4-trifluoromethylphenyl)pyrazolo-[4,3-d]-pyrimidine;

1,3-dimethyl-5-(4-aminophenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(3-aminophenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(3-nitrophenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(2-methoxyphenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(3,4-dichlorophenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(3,4-dimethoxyphenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(2,4-dimethoxyphenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(2-nitro-4-chlorophenyl)pyrazolo-[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(2-amino-4-chlorophenyl)pyrazolo-[4,3-d]-pyrimidine-7-one;

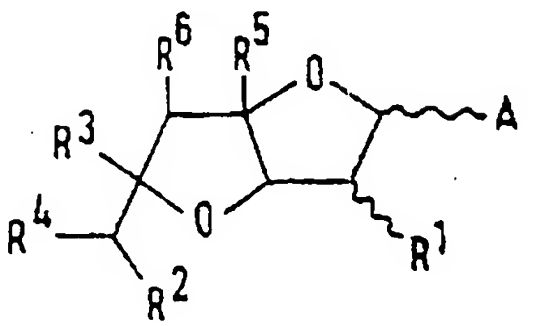
1,3-dimethyl-5-(4-sulfonic acid phenyl)pyrazolo-[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-[4-(N-2-(dimethylamino)ethyl)-benzenesulfonamide]pyrazolo[4,3-d]pyrimidine-7-one;

1,3-dimethyl-5-(3,5-dimethoxyphenyl)pyrazolo[4,3-d]-pyrimidine-7-one; or

1,3-dimethyl-5-(3-methoxyphenyl)pyrazolo[4,3-d]-pyrimidine-7-one.

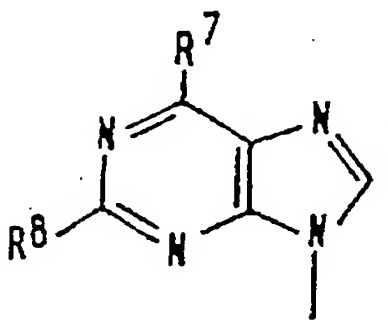
European published application number 0214708, which discloses compounds of the formula

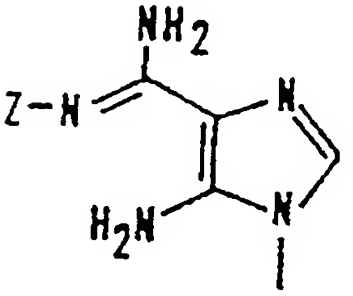


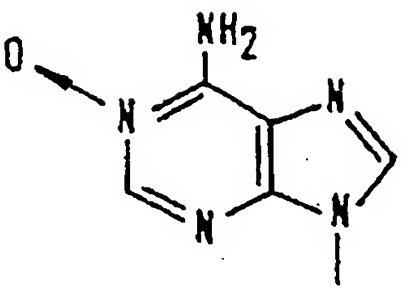
(I)

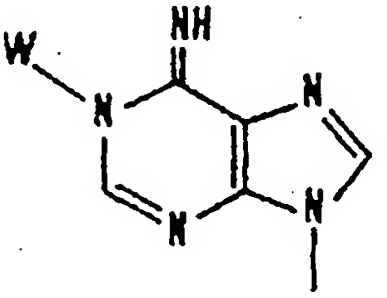
in which:

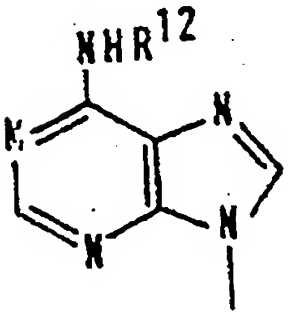
A represents a group of formula:

(a) 

(b) 

(c) 

(d) 

or (e)  ;

R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom or a group of formula $-OR^9$;

R^3 and R^4 are the same or different and each represents a carbamoyl group or a carboxy group;

R^5 and R^6 both represent hydrogen atoms or together they represent an extra carbon-carbon bond between the carbon atoms to which they are attached;

R' represents a hydrogen atom, a halogen atom or a group of formula -OR', -NR''R'' or -SR';

R' represents a halogen atom or a group of formula -OR', -NR''R'' or -SR';

R' represents a hydrogen atom, a C_1-C_4 alkyl group, an alkylsulphonyl group, a haloalkylsulphonyl group, an arylsulphonyl group or a hydroxy-protecting group;

R'' and R'' are the same or different and each represents a hydrogen atom, a hydroxy group, a C_1-C_4 alkyl group, a C_1-C_4 hydroxyalkyl group, a C_1-C_4 aminoalkyl group, an aralkyl group, an aryl group, a C_1-C_4 alkoxy group, an aralkyloxy group, an amino group, a C_1-C_{20} aliphatic acyl group or an aromatic acyl group; or R'' and R'' together represent a substituted methylene group, or R'' and R'', together with the nitrogen atom to which they are attached, represent a heterocyclic group having 5 or 6 ring atoms, of which, in addition to the nitrogen atom shown, 0 or 1 are additional oxygen, nitrogen or sulphur hetero-atoms, said heterocyclic group being unsubstituted or having from 1 to 3 C_1-C_4 alkyl and/or C_1-C_4 alkoxy substituents;

R'' represents a C_1-C_4 alkyl group;

Z represents a hydrogen atom, a hydroxy group or a substituted hydroxy group; and

W represents an alkoxy group or an aralkoxy group;

provided that, when A represents said group of formula (e), R' and R' both represent hydrogen atoms;

and pharmaceutically acceptable salts and esters thereof.

Preferred compounds include:

2-Amino-6-desamino-6-hydroxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-6-desamino-6-hydroxygriseolic acid 7'-amide and pharmaceutically acceptable salts and esters thereof.

2-Aminogriseolic acid and pharmaceutically acceptable salts and esters thereof.

Bis(pivaloyloxymethyl) 2-amino-6-desamino-6-hydroxygriseolate and pharmaceutically acceptable salts thereof.

2-Amino-N 6'-methoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-N6'-benzyloxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Fluorogriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Chlorogriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-6-desamino-6-hydroxy-7'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-7'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Chloro-7'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-6-desamino-6-hydroxy-2'-chloro-2'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-6-desamino-6-hydroxy-2'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-2'-chloro-2'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-2'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Chloro-2'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

Griseolic acid N1'-oxide and pharmaceutically acceptable salts thereof.

2-Acetylamino-6-desamino-6-hydroxy-4',5'-dihydrogriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-6-desamino-6-hydroxy-4',5'-dihydrogriseolic acid and pharmaceutically acceptable salts and esters thereof.

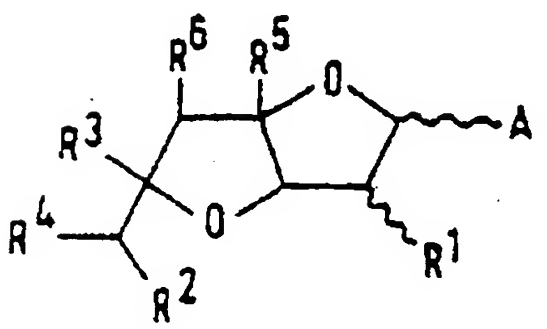
2-Acetylamino-6-desamino-6-hydroxy-4',5'-dihydro-7'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-6-desamino-6-hydroxy-4',5'-dihydro-7'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2,6-Dichloro-6-desamino-4',5'-dihydrogriseolic acid and pharmaceutically acceptable salts and esters thereof.

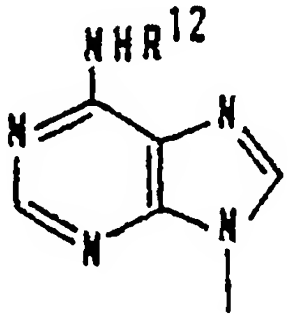
2-Chloro-4',5'-dihydrogriseolic acid and pharmaceutically acceptable salts and esters thereof.

European published application number 0319050, which discloses compounds of the formula



(I)

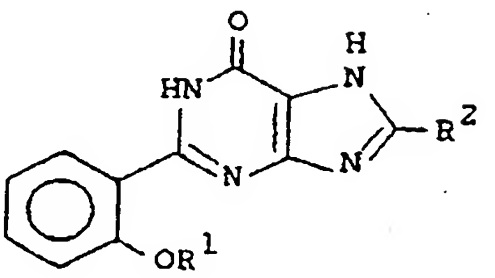
in which:
A represents a group of formula:



;

R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom or a group of formula $-OR^9$;
R^3 and R^4 are the same or different and each represents a carbamoyl group or a carboxy group;
R^5 and R^6 both represent hydrogen atoms;
R^9 represents a hydrogen atom, a C_1-C_6 alkyl group, an alkylsulphonyl group, a haloalkylsulphonyl group, an arylsulphonyl group or a hydroxy-protecting group;
R^{12} represents a C_1-C_6 alkyl group;
and pharmaceutically acceptable salts and esters thereof.

European published application number 0293063, which discloses compounds of the formula



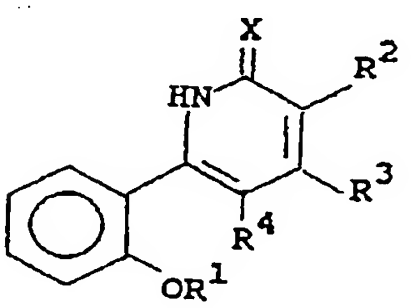
(1)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl or C_{2-6}alkenyl, and
R^2 is hydrogen or hydroxy.

Preferred compounds include:

2-(2-propoxyphenyl)-6-purinone,
2-(2-ethoxyphenyl)-6-purinone,
2-(2-butoxyphenyl)-6-purinone,
2-(2-isobutoxyphenyl)-6-purinone,
2-(2-propoxyphenyl)purine-6,8-dione,
2-(2-methoxyphenyl)purine-6,8-dione,
2-(2-ethoxyphenyl)purine-6,8-dione,
2-(2-butoxyphenyl)purine-6,8-dione,
2-(2-isobutoxypheny)purine-6,8-dione, or
2-(2-allyloxyphenyl)purine-6-8-dione
or a pharmaceutically acceptable salt thereof.

European published application number 0347027, which discloses compounds of the formula



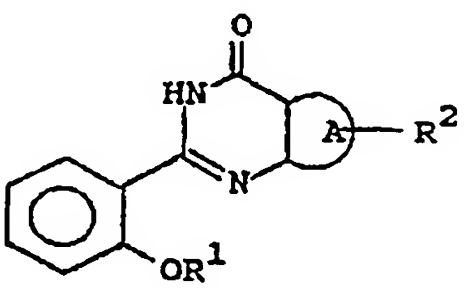
(1)

or a pharmaceutically acceptable salt thereof, wherein
X is O or S;
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkylC_{1-4}alkyl, or C_{1-4}alkyl substituted by 1 to 6 fluoro groups;
R^2 is hydrogen, -CN, $-CONR^5R^6$, $-CO_2R^7$, 5-tetrazolyl, $-NO_2$, $-NH_2$ or $-NHCOR^8$ wherein R^5, R^6, R^7 and R^8 are independently hydrogen or C_{1-4}alkyl;
R^3 is hydrogen or C_{1-4}alkyl; and
R^4 is hydrogen or C_{1-4}alkyl;
with the proviso that R^1 is not methyl when R^2 is $-CO_2H$, $-CO_2CH_2CH_3$ or -CN, X is O, R^3 is hydrogen and R^4 is hydrogen or methyl.

Preferred compounds include:

3-cyano-6-(2-propoxyphenyl)-2(1H)-pyridinone,
6-(2-propoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide,
6-(2-propoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxylic acid,
methyl 6-(2-propoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxylate,
6-(2-propoxyphenyl)-3-(1H-tetrazol-5-yl)-2(1H)-pyridinone,
6-(2-propoxyphenyl)-2(1H)-pyridinone,
3-nitro-6-(2-propoxyphenyl)-2(1H)-pyridinone,
3-cyano-6-(2-ethoxyphenyl)-2(1H)-pyridinone ,
3-amino-6-(2-propoxyphenyl)-2(1H)-pyridinone,
3-cyano-4-methyl-6-(2-propoxyphenyl)-2(1H)-pyridinone,
3-cyano-5-methyl-6-(2-propoxyphenyl)-2(1H)-pyridinone,
3-cyano-6-(2-(1,1,2,3,3,3-hexafluoropropoxy)phenyl-2(1H)-pyridinone,
3-cyano-6-(2-propoxyphenyl)-2(1H)-pyridinethione,
1,2-dihydro-4-methyl-2-oxo-6-(2-propoxyphenyl)pyridine-3-carboxylic acid,
methyl 1,2-dihydro-4-methyl-2-oxo-6-(2-propoxyphenyl)-pyridine-3-carboxylate,
1,2-dihydro-4-methyl-2-oxo-6-(2-propoxyphenyl)pyridine-3-carboxamide,
3-cyano-6-(2-cyclopropylmethoxyphenyl)-2(1H)-pyridinone,
6-(2-butoxyphenyl)-3-cyano-2(1H)-pyridinone,
6-(2-allyloxyphenyl)-3-cyano-2(1H)-pyridinone,
3-cyano-6-[2-(2-methylpropoxy)phenyl]-2(1H)-pyridinone,
6-(2-ethoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide,
6-(2-cyclopropylmethoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide,
6-(2-butoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide,
6-(2-allyloxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide, or
6-[2-(2-methylpropoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide,
or a pharmaceutically acceptable salt thereof.

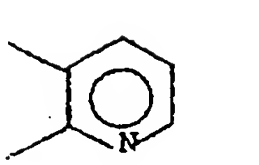
European published application number 0347146, which discloses compounds of the formula



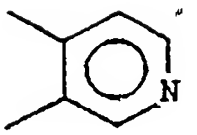
(1)

or a pharmaceutically acceptable salt thereof, wherein

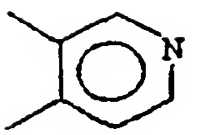
is a ring of sub-formula (a), (b), (c), (d), (e), (f) or (g) :



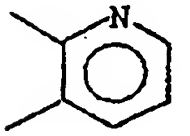
(a)



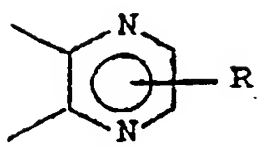
(b)



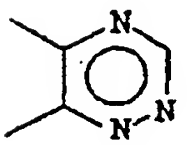
(c)



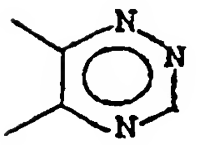
(d)



(e)



(f)



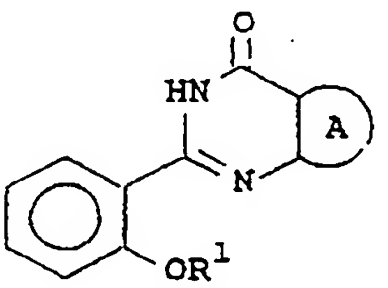
(g),

R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, or C_{1-6}alkyl substituted by 1 to 6 fluoro groups;
R^2 is C_{1-5}alkylthio, C_{1-6}alkylsulphonyl, C_{1-5}alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6}alkyl, phenyl, -NHCOR^3 wherein R^3 is hydrogen or C_{1-6}alkyl, or -NR^{4}R^5 wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5}cycloalkyl or C_{1-6}alkyl which is optionally substituted by -CF_3, phenyl, -S(O)$_n$C$_{1-6}$alkyl wherein n is 0, 1 or 2, -OR^6, -CO_2R^7 or -NR^{8}R^9 wherein R^6 to R^9 are independently hydrogen or C_{1-6}alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said -S(O)$_n$C$_{1-6}$alkyl, -OR^6 or -NR^{8}R^9 groups; and
R is hydrogen and can also be hydroxy when R^2 is hydroxy.

Preferred compounds include:

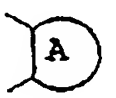
2-(2-propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[3,4-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[4,3-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[3,2-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pteridin-4(3H)-one,
2-(2-propoxyphenyl)pteridin-4,6(3H,5H)-dione,
2-(2-propoxyphenyl)pteridin-4,6,7(3H,5H,8H)-trione,
5,6-dihydro-3-methylthio-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e] [1,2,4]triazine,
3-amino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methylamino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methoxy-5,6-dihydro-5-oxo-7-)2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-amino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methoxy-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3,8-dioxo-6-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-e][1,2,4]triazine,
3-dimethylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-allyloxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-isobutoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-cyclopropylmethoxyphenyl)-7,8dihydropyrimido[4,5-e][1,2,4]triazine or
3-methylthio-8-oxo-6-(2-methoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine
or a pharmaceutically acceptable salt thereof.

European published application number 0349239, which discloses compounds of the formula

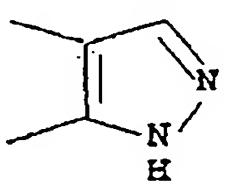


(1)

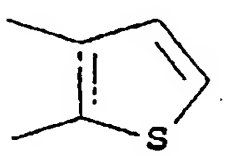
or a pharmaceutically acceptable salt thereof, wherein



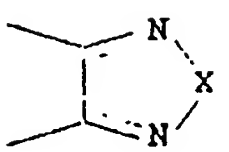
is a ring of sub-formula (a), (b) or (c):



(a)



(b)



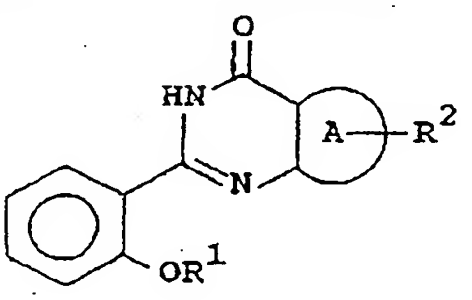
(c),

X is oxygen or sulphur, and
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-4}alkyl, or C_{1-4}alkyl substituted by 1 to 6 fluoro groups.

Preferred compounds include:

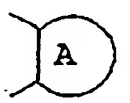
6-(2-propoxyphenyl)pyrazolo[3,4-d]pyrimidin-4(5H)-one,
2-(2-propoxyphenyl)thieno[2,3-d]pyrimidin-4(3H)-one,
2-(2-propoxyphenyl)[1,2,5]oxadiazolo[3,4-d]pyrimidin-4(3H)-one, or
2-(2-propoxyphenyl)[1,2,5]thiadiazolo[3,4-d]pyrimidin-4(3H)-one,
or a pharmaceutically acceptable salt thereof.

European published application number 0351058, which discloses compounds of the formula

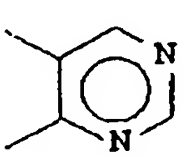


(1)

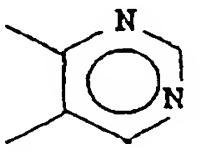
or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, or C_{1-6}alkyl substituted by 1 to 6 fluoro groups;
R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6}alkyl, phenyl, $-NHCOR^3$ wherein R^3 is hydrogen or C_{1-6}alkyl, or $-NR^4R^5$, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5}cycloalkyl or C_{1-6}alkyl which is optionally substituted by $-CF_3$, phenyl, $-S(O)_nC_{1-6}$alkyl wherein n is 0, 1 or 2, $-OR^6$, $-CO_2R^7$ or $-NR^8R^9$ wherein R^6 to R^9 are independently hydrogen or C_{1-6}alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said $-S(O)_nC_{1-6}$alkyl, $-OR^6$ or $-NR^8R^9$ groups; and



is a ring of sub-formula (a) or (b) :



(a)



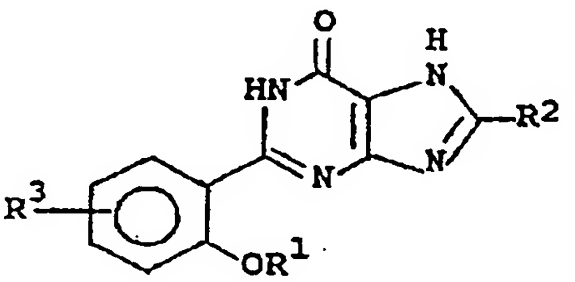
(b).

Preferred compounds include:

7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-methylthio-2-(2-ethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-methylthio-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-methylthio-2-(2-isobutoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-methylthio-2-(2-cyclopropylmethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-methylthio-2-(2-allyloxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-amino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-methylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-dimethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-hydrazino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-ethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-ethyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine
7-methylamino-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-phenyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,

7-morpholino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-cyclopropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-acetamido-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-propylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(3-hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-methoxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-dimethylaminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(3-methylthiopropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-aminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine hydrochloride,
7-(3-methylsulphinylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(3-methylsulphonylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
4,7-dioxo-2-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-d]pyrimidine,
7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-diethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-ethoxycarbonylethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(ethoxycarbonylmethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-carboxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(carboxymethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-ethoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-methoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2,2,2-trifluoroethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-propoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(N-ethyl-N-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-dipropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-phenethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine, or
4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[5,4-d]pyrimidine,
or a pharmaceutically acceptable salt thereof.

European published application number 0352960, which discloses compounds of the formula



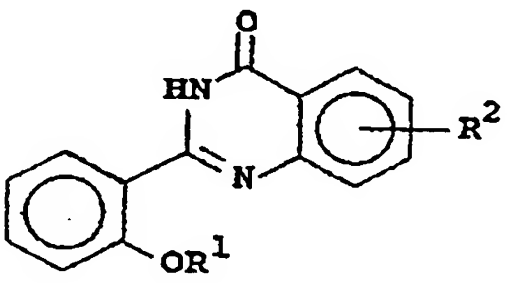
(1)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-4}alkyl, phenylC_{1-4}alkyl or C_{1-4}alkyl substituted by 1 to 6 fluoro groups;
R^2 is hydrogen, hydroxy, C_{1-4}alkyl, phenyl, mercapto, C_{1-4}alkylthio, CF_3 or amino;
R^3 is hydrogen, nitro, amino, C_{1-4}alkanoylamino, C_{1-4}-alkoxy, C_{1-4}alkyl, halo, $SO_2NR^4R^5$, $CONR^4R^5$, cyano or C_{1-4}alkylS(O)n;
R^4 and R^5 are independently hydrogen or C_{1-4}alkyl; and
n is 0, 1 or 2;
provided that R^3 is not hydrogen when R^1 is C_{1-6}alkyl or C_{2-6}alkenyl and R^2 is hydrogen or hydroxy.

Preferred compounds include:

2-(2-[2,2,2-trifluoroethoxy]phenyl)purin-6-one,
2-(2-cyclopropylmethoxyphenyl)purin-6-one,
2-(2-cyclopropylmethoxyphenyl)purin-6,8-dione,
2-(2-benzyloxyphenyl)purin-6,8-dione,
2-(2-propoxyphenyl)-8-trifluoromethylpurin-6-one,
2-(2-propoxyphenyl)-8-phenylpurin-6-one,
2-(2-propoxyphenyl)-8-methylpurin-6-one,
2-(2-propoxyphenyl)-8-mercaptopurin-6-one,
2-(2-propoxyphenyl)-8-methylthiopurin-6-one,
2-(2-propoxyphenyl)-8-aminopurin-6-one,
2-(2-propoxy-5-nitrophenyl)purin-6-one,
2-(2-propoxy-5-aminophenyl)purin-6-one,
2-(2-propoxy-5-acetamidophenyl)purin-6-one,
2-(2-propoxy-4-methoxyphenyl)purin-6-one,
2-(2-propoxy-5-methoxyphenyl)purin-6-one,
2-(2-propoxy-5-chlorophenyl)purin-6-one,
2-(2-propoxy-4-methylphenyl)purin-6-one,
2-(2-propoxy-5-fluorophenyl)purin-6-one,
2-(2-propoxy-5-dimethylsulphamoylphenyl)purin-6-one,
2-(2-propoxy-5-methylsulphamoylphenyl)purin-6-one,
2-(2-propoxy-5-sulphamoylphenyl)purin-6-one,
2-(2-propoxy-4-methylthiophenyl)purin-6-one,
2-(2-propoxy-5-cyanophenyl)purin-6-one, or
2-(2-propoxy-5-carbamoylphenyl)purin-6-one,
or a pharmaceutically acceptable salt thereof.

European published application number 0371731, which discloses compounds of the formula



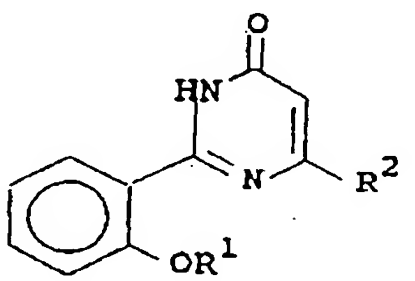
(1)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-4}alkyl, phenylC_{1-4}alkyl or C_{1-4}alkyl substituted by 1 to 6 fluoro groups;
R^2 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkoxy, nitro or $-NR^3R^4$; and
R^3 and R^4 are independently hydrogen or C_{1-4}alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy;
with the proviso that R^1 is not methyl or ethyl when R^2 is hydrogen.

Preferred compounds include:

2-(2-propoxyphenyl)quinazolin-4(3H)-one,
7-methylthio-2-(2-propoxyphenyl)quinazolin-4(3H)-one,
7-nitro-2-(2-propoxyphenyl)-4(3H)-quinazolinone,
7-amino-2-(2-propoxyphenyl)-4(3H)-quinazolinone, or
7-methylamino-2-(2-propoxyphenyl)-4(3H)-quinazolinone
or a pharmaceutically acceptable salt thereof.

European published application number 0395328, which discloses compounds of the formula



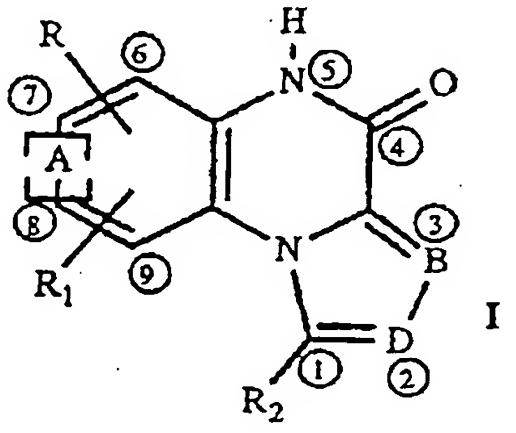
(1)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, phenylC_{1-6}alkyl or C_{1-6}alkyl substituted by 1 to 6 fluoro groups; and
R^2 is C_{1-6}alkyl, phenyl, hydroxy, C_{1-6}alkoxy, halo, -NHCOR^3, -NHCONHR^4, 5-tetrazolyl, -CO_2R^5, cyano, -CONR^{6}R^7, or -NR^{8}R^9 wherein R^3 to R^7 are independently hydrogen or C_{1-6}alkyl and R^8 and R^9 are independently hydrogen or C_{1-6}alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy;

Preferred compounds include:

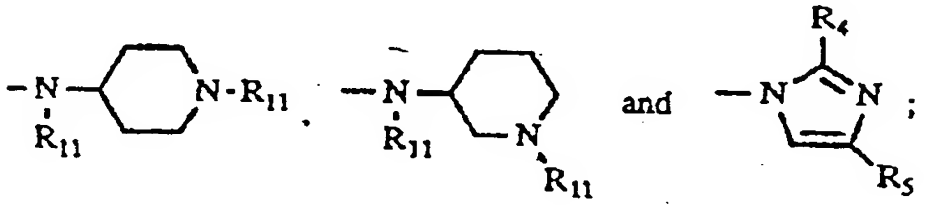
6-amino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-acetamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-propionamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-butyramido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-N'-methylureido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
4,6-dihydroxy-2-(2-propoxyphenyl)pyrimidine,
4-chloro-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
6-ethylamino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-propylamino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-(2-hydroxyethylamino)-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-(3-hydroxypropylamino)-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
4-hydroxy-6-methyl-2-(2-propoxyphenyl)pyrimidine,
6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxylic acid,
ethyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxylate,
6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
4-cyano-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
2-(2-propoxyphenyl)-6-(1H-tetrazol-5-yl)pyrimidin-4(3H)-one,
4-ethyl-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
4-hydroxy-6-phenyl-2-(2-propoxyphenyl)pyrimidine,
N-methyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
N-ethyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
N-propyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
6-ethoxy-2-(2-propoxyphenyl)pyrimidin-4(3H)-one, or
6-N,N-bis-(2-hydroxyethyl)amino-2-(2-propoxyphenyl)pyrimidin-4(3H)-one,
or a pharmaceutically acceptable salt thereof.

European published application number 0400583, which discloses compounds of the formula

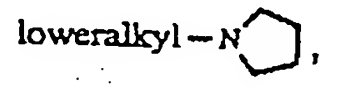


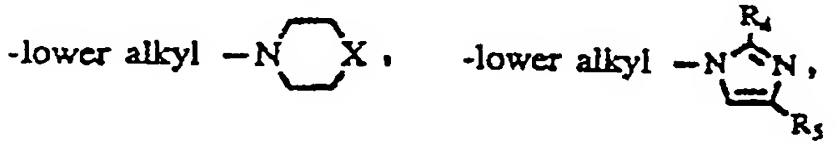
I

wherein -
A is N or CH;
B is N CR_3;
D is N or CR_2;
R, R_1, are the same or independently hydrogen, hydroxy, loweralkyl, lower alkoxy, phenyloxy, $R_6S(O)_n$-, W-ALK-Q-,

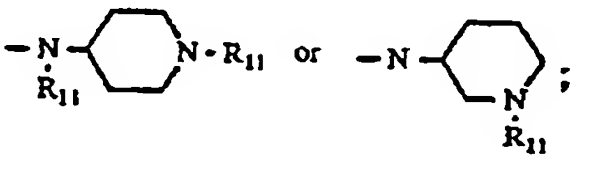


R_2 is hydrogen, lower alkyl, phenyl which may be substituted by up to three methoxy groups, lower alkyl substituted by phenyl which may be substituted by up to three methoxy groups, - lower alkyl -$N(R_8)_2$,

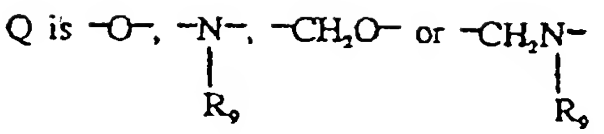


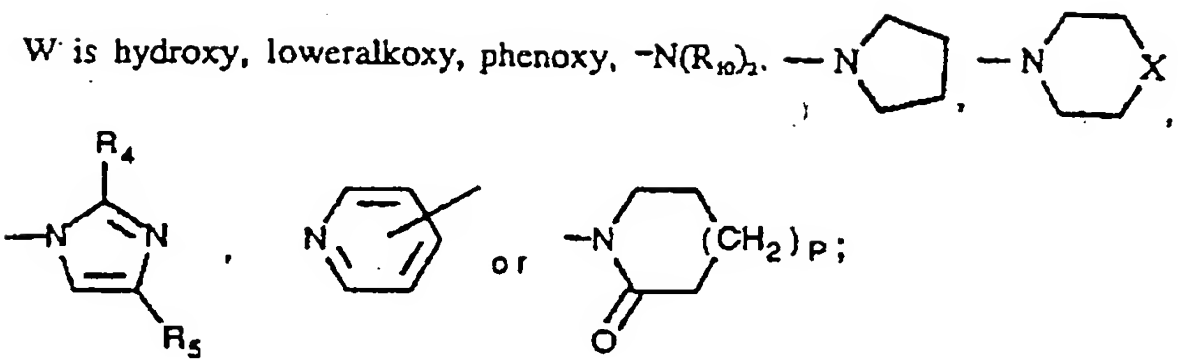


pyridinyl or lower-alkyl pyridinyl;
R_3 is hydrogen, lower alkyl, phenyl, lower alkylphenyl, pyridinyl or loweralkyl pyridinyl;
R_4, R_5 are the same or independently hydrogen or lower alkyl;
R_6 is lower alkyl, phenyl, lower alkylphenyl or pyridinyl;
R_7 are the same or independently hydrogen, loweralkyl, phenyl, pyridinyl,

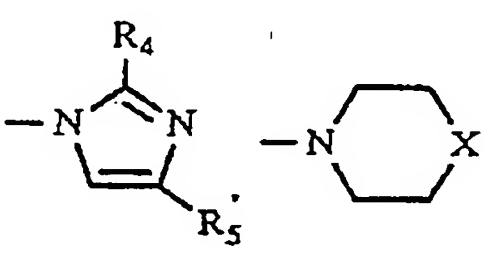


R_8 are the same or independently lower alkyl, phenyl or pyridinyl;

Q is 

W is hydroxy, loweralkoxy, phenoxy, 

ALK is a C_1-C_4 straight or branched chain alkyl;
R_9 is hydrogen, lower alkyl or phenyl;
R_{10} are the same or independently hydrogen, loweralkyl or phenyl;
R_{11} are the same or independently hydrogen or lower alkyl;
X is $-CH_2-$, $-O-$, $S(O)_n$, $-NR_{10}$;
n is the integer 0, 1 or 2 and
p is the integer 0 or 1.
with the provisos that:
a) one and only one of B or D must be N;
b) when A is CH, when D is N, when B is CR_3 where R_3 is H, when R_2 is hydrogen, lower alkyl or phenyl then R and/or R_1 must be



or W-ALK-Q-;
and the pharmaceutically acceptable salts thereof.

Preferred compounds include:

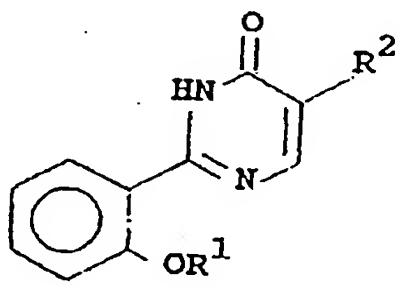
1-ethyl-8-(1H-imidazol-1-yl)-3-methylimidazo[1,5-a]quinoxalin-4-(5H)-one,1-ethyl-8-(1H-imidazol-1-yl)imidazo[1,5-a]quinoxalin-4(5H)-one, 1-ethyl-3-methyl-8-(4-morpholino)-imidazo [1,5-a]quinoxalin-4(5H)-one; 1-ethyl-8-(2-ethyl-4-methyl-1H-imidazol-1-yl)-3-methylimidazo[1,5-a]-quinoxalin-4(5H)-one 1-methyl-8-(2-methyl-1H-imidazol-1-yl)imidazo[1,5a]quinoxalin-4(5H)-one, 8-(1H-imidazol-1-yl)-1-methyl-imidazo[1,5-a]quinoxalin-4(5H)-one, 1-ethyl-3-methyl-8-(pyrrolidin-1-yl)imidazo[1,5-a]quinoxalin-4(5H)-one, 1-((morpholin-4-yl)methyl)imidazo[1,5-a]quinoxalin-4(5H)-one, or 6-ethoxy-1-ethyl-8-(2-ethyl-4-methyl-1H-imidazol-1-yl)-3-methylimidazo[1,5-a]quinoxalin-4(5H)-one,

8-(1H-imidazol-1-yl)imidazo[1,2a]quinoxalin-4(5H)-one imidazo[1,2-a]-quinoxalin-5-(4H)-one, or 2-methylimidazo[1,2-a]quinoxalin-4(5H)-one,

9-ethylimidazo[1,5-a] pyrido[3,2e]pyrazin-6(5H)-one, 9-methyl-2(2-methyl-1H-imidazol-1-yl) imidazo[1,5-a]pyrido [3,2-e]pyrazin-5(6H)-one, 9[(2-ethyl-1H- imidazol-1-yl)methyl]-imidazo[1,5-a]pyrido[3,2-e]pyrazin-6(5H)-one, or 1-ethylimidazo[1,5-a]pyrido[4,3-e]-pyrazin-4-(5H)-one,

imidazo[1,2-a]pyrido[3,2-e]pyrazin-6(5H)-one, 2-phenylimidazo[1,2-a]-pyrido[2,3-e]pyrazin-4(5H)-one, or 2-(1H-imidazol-1-yl)imidazo[1,2-a]pyrido[3,2-e]pyrazin-6(5H)-one.

European published application number 0400799, which discloses compounds of the formula



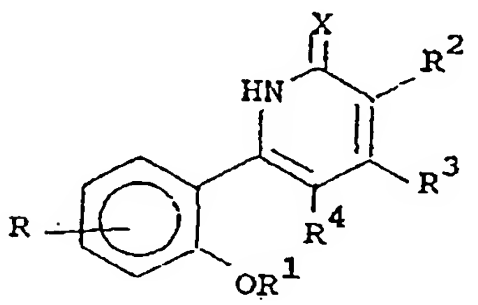
(1)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, phenylC_{1-6}alkyl or C_{1-6}alkyl substituted by 1 to 6 fluoro groups; and
R^2 is hydrogen, amino, -NHCOR^3, or -CONR^{4}R^5, wherein R^3 is C_{1-6}alkyl, R^4 is C_{1-6}alkyl and R^5 is hydrogen or C_{1-6}alkyl.

Preferred compounds include:

1,6-dihydro-6-oxo-2-(2-propoxyphenyl)pyrimidine-5-carboxamide,
N-methyl 1,6-dihydro-6-oxo-2-(2-propoxyphenyl)pyrimidine-5-carboxamide,
N,N-dimethyl 1,6-dihydro-6-oxo-2-(2-propoxyphenyl)pyrimidine-5-carboxamide,
5-amino-2-(2-propoxyphenyl)pyrimidin-4(3H)-one,
5-acetamido-2-(2-propoxyphenyl)pyrimidin-4(3H)-one, or
2-(2-propoxyphenyl)pyrimidin-4(3H)-one,
or a pharmaceutically acceptable salt thereof.

European published application number 0428268, which discloses compounds of the formula



(1)

or a pharmaceutically acceptable salt thereof, wherein
X is O or S;
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-4}alkyl, or C_{1-4}alkyl substituted by 1 to 3 fluoro groups;

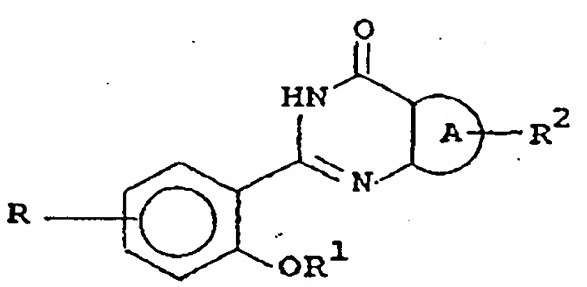
R^2 is hydrogen, -CN, $-CONR^5R^6$, $-CO_2R^7$,5-tetrazolyl, $-NO_2$, $-NH_2$ or $-NHCOR^8$ wherein R^5 to R^8 are independently hydrogen or C_{1-4}alkyl;
R^3 is hydrogen or C_{1-4}alkyl;
R^4 is hydrogen or C_{1-4}alkyl; and
R is halo, C_{1-4}alkyl, C_{1-4}alkoxy, cyano, $-CONR^9R^{10}$, $-CO_2R^{11}$, $-S(O)_nC_{1-4}$alkyl, $-NO_2$, $-NH_2$, $-NHCOR^{12}$, or $-SO_2NR^{13}R^{14}$ wherein n is 0, 1 or 2 and R^9 to R^{14} are independently hydrogen or C_{1-4}alkyl;
with the proviso that R^1 is not methyl when R^2 is $-CO_2H$, $-CO_2CH_2CH_3$ or -CN, X is O, R^3 is hydrogen, R^4 is hydrogen or methyl and R is 6-methoxy.

Preferred compounds include:

3-cyano-6-(2-methoxy-4-methylthiophenyl)-2(1H)-pyridinone,
3-cyano-6-(4-methylthio-2-propoxyphenyl)-2(1H)-pyridinone,
1,2-dihydro-6-(4-methylthio-2-propoxyphenyl)-2-oxo-3-pyridine carboxamide,
3-cyano-6-(2-methoxy-4-methylsulphinylphenyl)-2(1H)-pyridinone,
3-cyano-6-(4-methylsulphinyl-2-propoxyphenyl)-2(1H)-pyridinone,
3-cyano-6-(4-methylsulphonyl-2-propoxyphenyl)-2(1H)-pyridinone,
3-cyano-6-(2-methoxy-4-methylsulphonylphenyl)-2(1H)-pyridinone,
3-cyano-6-(5-fluoro-2-propoxyphenyl)-2(1H)-pyridinone,
1,2-dihydro-6-(5-fluoro-2-propoxyphenyl)-2-oxo-3-pyridine carboxamide,
3-cyano-6-(4-methoxy-2-propoxyphenyl)-2(1H)-pyridinone,
1,2-dihydro-6-(4-methoxy-2-propoxyphenyl)-2-oxo-3-pyridine carboxamide,
3-cyano-6-(5-methoxy-2-propoxyphenyl)-2(1H)-pyridinone,
1,2-dihydro-6-(5-methoxy-2-propoxyphenyl)-2-oxo-3-pyridine carboxamide,
3-cyano-6-(5-cyano-2-propoxyphonyl)-2(1H)-pyridinone,
3-(3-carboxamido-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxybenzamide,
methyl 3-(3-cyano-1,2-dihydro-(2-oxo-6-pyridinyl)-4-propoxybenzoate,
3-(3-cyano-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxybenzamide,
N-methyl-3-(3-cyano-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxybenzamide,
N-methyl 3-(3-carboxamido-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxybenzamide,
N,N-dimethyl-3-(3-cyano-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxybenzamide,
N,N-dimethyl 3-(3-carboxamido-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxybenzamide,
4-(3-cyano-1,2-dihydro-2-oxo-6-pyridinyl)-3-propoxybenzonitrile,
4-(3-carboxamido-1,2-dihydro-2-oxo-6-pyridinyl)-3-propoxybenzamide,

3-cyano-6-(5-methylthio-2-propoxyphenyl)-2(1H)pyridinone,
3-(3-cyano-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxy-N,N-dimethylbenzenesulphonamide,
3-(3-carboxamido-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxy-N,N-dimethylbenzenesulphonamide,
6-(2-cyclopropylmethoxy-5-flourophenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide,
6-(5-fluoro-2-(2-methylpropoxy)phenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide,
3-cyano-6-(5-nitro-2-propoxyphenyl)-2(1H)-pyridinone,
1,2-dihydro-6-(5-nitro-2-propoxyphenyl)-2-oxo-3-pyridinone carboxamide,
3-cyano-6-(5-amino-2-propoxyphenyl)-2(1H)-pyridinone,
1,2-dihydro-6-(5-amino-2-propoxyphenyl)-2-oxo-3-pyridinone carboxamide,
3-cyano-6-(5-acetamido-2-propoxyphenyl)-2(1H)-pyridinone or
1,2-dihydro-6-(5-acetamido-2-propoxyphenyl)-2-oxo-3-pyridine carboxamide,
or a pharmaceutically acceptable salt thereof.

European published application number 0442204, which discloses compounds of the formula

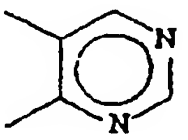


(1)

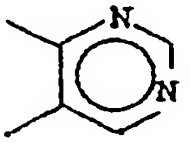
or a pharmaceutically acceptable salt thereof, wherein

R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkyl C_{1-6}alkyl, or C_{1-6}alkyl substituted by 1 to 6 fluoro groups ;
R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6}alkyl, phenyl, -$NHCOR^3$ wherein R^3 is hydrogen or C_{1-6} alkyl, or -NR^4R^5, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5}cycloalkyl or C_{1-6}alkyl which is optionally substituted by -CF_3, phenyl, -$S(O)_nC_{1-6}$ alkyl wherein
n is 0, 1 or 2, -OR^6, -CO_2R^7 or -NR^8R^9 wherein R^6 to R^9 are independently hydrogen or C_{1-6}alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said -$S(O)_nC_{1-6}$alkyl, -OR^6 or -NR^8R^9 groups ;
R is halo, C_{1-4}alkyl, C_{1-4}alkoxy, cyano, -$CONR^{10}R^{11}$, CO_2R^{12}, C_{1-4} alkyl$S(O)_n$, -NO_2, -NH_2, -$NHCOR^{13}$ or $SO_2NR^{14}R^{15}$ wherein n is 0, 1 or 2 and R^{10} to R^{15} are independently hydrogen or C_{1-4} alkyl ; and

is a ring of sub-formula (a) or (b) :

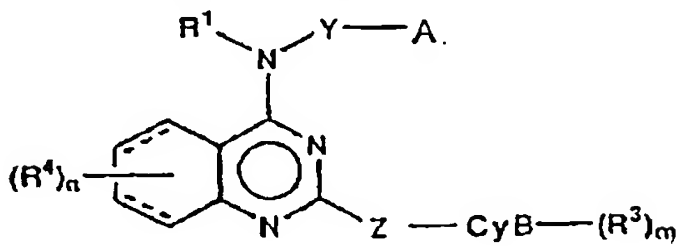


(a)



(b).

European published application number 0579496, which discloses compounds of the formula



(I)

wherein — represents a single or double bond;
R^1 is hydrogen or C_{1-4} alkyl;
Y is a single bond or C_{1-6} alkylene;
A is
(i) -CyA-$(R^2)_1$,
(ii) -O-R^0 or -$S(O)_p$-R^0, or
(iii) -$NR^{16}R^{17}$;
in which R^0 is hydrogen, C_{1-4} alkyl, hydroxy-C_{1-4} alkyl or -CyA-$(R^2)_1$;
R^{16} and R^{17} independently are hydrogen or C_{1-4} alkyl;
p is 0-2;
CyA is
(1) a 3-7 membered, saturated or unsaturated carbocycle,
(2) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom,
(3) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and one oxygen atom,
(4) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and two oxygen atoms,
(5) a 4-7 membered, unsaturated or partially saturated heterocycle containing two nitrogen atoms and one oxygen atom,
(6) a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two sulfur atoms,
(7) a 4-7 membered, unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms;
R^2 is (1) hydrogen, (2) C_{1-4} alkyl, (3) C_{1-4} alkoxy, (4) -$COOR^5$, in which R^5 is hydrogen or C_{1-4} alkyl, (5) -NR^6R^7, in which R^6 and R^7 independently are hydrogen or C_{1-4} alkyl, (6) -$SO_2NR^6R^7$, in which R^6 and R^7 are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro or (10) trifluoromethoxy;
Z is a single bond, methylene, ethylene, vinylene or ethynylene;
CyB is
(1) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom,
(2) a 4-7 membered, unsaturated or partially saturated heterocycle containing two nitrogen atoms,
(3) a 4-7 membered, unsaturated or partially saturated heterocycle containing three nitrogen atoms,
(4) a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two oxygen atoms,
(5) a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two sulfur atoms,
R^3 is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, halogen or trifluoromethyl;
R^4 is (1) hydrogen, (2) C_{1-4} alkyl, (3) C_{1-4} alkoxy, (4) -$COOR^8$, in which R^8 is hydrogen or C_{1-4} alkyl, (5) -NR^9R^{10}, in which R^9 is hydrogen, C_{1-4} alkyl or phenyl(C_{1-4} alkyl) and R^{10} is hydrogen or C_{1-4} alkyl, (6) -$NHCOR^{11}$, in which R^{11} is C_{1-4} alkyl, (7) -$NHSO_2R^{11}$, in which R^{11} is as hereinbefore defined, (8) $SO_2NR^9R^{10}$ in which R^9 and R^{10} are as hereinbefore defined, (9) -$OCOR^{11}$, in which R^{11} is as hereinbefore defined, (10) halogen, (11) trifluoromethyl, (12) hydroxy, (13) nitro, (14) cyano, (15) -$SO_2N{=}CHNR^{12}R^{13}$ in which R^{12} is hydrogen or C_{1-4} alkyl and R^{13} is C_{1-4} alkyl, (16) -$CONR^{14}R^{15}$ in which R^{14} is hydrogen or C_{1-4} alkyl or phenyl(C_{1-4} alkyl) and R^{15} is C_{1-4} alkyl or (17) C_{1-4} alkylthio, (18) C_{1-4} alkylsulfinyl, (19) C_{1-4} alkylsulfonyl, (20) ethynyl, (21) hydroxymethyl, (22) tri(C_{1-4} alkyl)silylethynyl or (23) acetyl;
and l, m and n independently are 1 or 2;
with the proviso that
(1) CyA-$(R^2)_1$ does not represent cyclopentyl or trifluoromethylphenyl when Y is a single bond,
(2) CyB does not bond to Z through a nitrogen atom when Z is vinylene or ethynylene,
(3) CyB is not pyridine or thiophene when CyA is a 4-7 membered unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms, and
(4) Y is not a single bond when A is (ii) -O-R^0 or -$S(O)_p$-R^0 or (iii) -$NR^{16}R^{17}$;
or a pharmaceutically acceptable salt thereof, or a hydrate thereof.

Preferred compounds include:

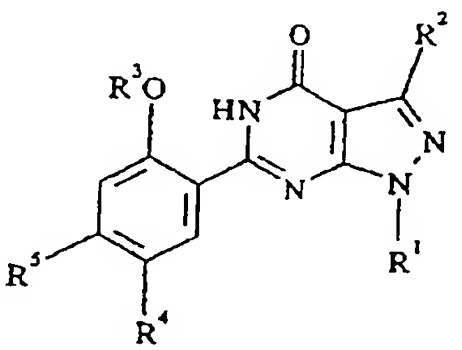
4-phenylmethylamino-2-(3-pyridyl)quinazoline,
4-(3-methylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3,4-dimethoxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(4-carboxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-methoxycarbonylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(4-(N,N-dimethylamino)phenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(4-sulfamoylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-chlorophenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-nitrophenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-2-(6-methyl-3-pyridyl)quinazoline,
4-phenylmethylamino-2-(6-methoxy-3-pyridyl)quinazoline,
4-phenylmethylamino-2-(6-chloro-3-pyridyl)quinazoline,
4-phenylmethylamino-2-(6-trifluoromethyl-3-pyridyl)quinazoline,
4-phenylmethylamino-6-methyl-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-methoxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6,7-dimethoxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-carboxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-methoxycarbonyl-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-amino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-(N,N-dimethylamino)-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-acetylamino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-methanesulfonylamino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-sulfamoyl-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-acetoxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-bromo-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-trifluoromethyl-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-trifluoromethoxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-hydroxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-nitro-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-cyano-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-methyl-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-methoxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6,7-dimethoxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-carboxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-methoxycarbonyl-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-amino-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-(N,N-dimethylamino)-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-acetylamino-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-methanesulfonylamino-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-sulfamoyl-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-acetoxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-chloro-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-bromo-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-7-fluoro-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-trifluoromethyl-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-trifluoromethoxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-hydroxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-nitro-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-cyano-2-(4-pyridyl)quinazoline,
4-phenylamino-2-(3-pyridyl)quinazoline,
4-(3-methoxycarbonylphenyl)amino-2-(3-pyridyl)quinazoline,
4-phenylethylamino-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-2-(2-pyridyl)quinazoline,
4-phenylmethylamino-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-2-(2-(3-pyridyl)ethyl)quinazoline,
4-phenylmethylamino-2-(2-(3-pyridyl)vinyl)quinazoline,
6-iodo-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
4-(3-carboxyphenyl)amino-2-(4-pyridyl)quinazoline,
6-fluoro-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
4-(cyclopropylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(cyclohexylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(2-azepinylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-pyridylmethyl)amino-2-(3-pyridyl)quinazoline,
4-((1-methyl-2-pyrrolyl)methyl)amino-2-(3-pyridyl)quinazoline,
4-(3-isoxazolyl)amino-2-(3-pyridyl)quinazoline,
4-(3-isoxazolylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(2-thienylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(2-furylmethyl)amino-2-(1 -imidazolyl)quinazoline,
4-(2-tetrahydrofuranylmethyl)amino-2-(1 -imidazolyl)quinazoline,
4-(4-tetrahdyropyranylmethyl)amino-2-(1 -imidazolyl)quinazoline,
6-methoxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,
6-chloro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,
4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,
4-(2-thienylmethyl)amino-2-(1 -imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
4-(1,1-dimethyl-2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
6-methoxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
6-chloro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
4-(3-ethoxypropyl)amino-2-(1-imidazolyl)quinazoline,
6-nitro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
6-chloro-4-(2-ethoxyethyl)amino-2-(3-pyridyl)quinazoline,
6,7-dimethoxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
6-chloro-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
6-chloro-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)quinazoline,
6-methoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-iodo-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-methoxy-2-(2-methyl-1-imidazolyl)quinazoline,
4-(2-hydroxyethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6,8-diiodo-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-6-iodo-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-methylsulfinyl-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-methylsulfonyl-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylsulfinyl-2-(1-imidazolyl)-quinazoline,
2-(1-imidazolyl)-4-(2-methoxyethyl)amino-6-(2-triethylsilylethynyl)quinazoline,
6-acetyl-4-(2-methoxyethyl)amino-2-(3-pyridyl)quinazoline,
6-ethynyl-4-(2-methoxyethyl)amino-2-(3-pyridyl)quinazoline,
4-[2-(2-hydroxyethoxy)ethyl]amino-6-acetyl-2-(1-imidazolyl)quinazoline,
4-(2-methylthioethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(2-methylsulfinylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(2-methylsulfonylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-[2-(2-hydroxyethoxy)ethyl]amino-6-methoxycarbony1-2-(-imidazolyl)-quinazoline,
4-[2-(2-hydroxyethoxy)ethyl]amino-6-hydroxymethyl-2-(1-imidazolyl)-quinazoline,
4-(2-methoxyethyl)amino-6-hydroxymethyl-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-G-methoxycarbonyl-2-(1-imidazolyl)quinazoline,
4-(3-methoxypropyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline,
2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-(2-triisopropyl- silylethynyl)-quinazoline,
2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-ethynylquinazoline,
4-phenylmethylamino-6-methyl-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6,7-dimethoxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-carboxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-methoxycarbonyl-2-(1-imidazolyl)quinazoline,

4-phenylmethylamino-6-amino-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-(N,N-dimethylamino)-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-acetylamino-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-methanesulfonylamino-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-sulfamoyl-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-acetoxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-bromo-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-7-fluoro-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-trifluoromethyl-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-trifluoromethoxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-hydroxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-nitro-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-cyano-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-2-((1-imidazolyl)methyl)quinazoline,
4-phenylmethylamino-2-(2-methyl-1 -imidazolyl)quinazoline,
6-bromo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
7-chloro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-chloro-4-phenylamino-2-(1-imidazolylmethyl)quinazoline,
6-nitro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-methoxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-chloro-4-phenylmethylamino-2-(1-imidazolylmethyl)quinazoline,
6-chloro-4-(3-carboxyphenyl)amino-2-(1 -imidazolylmethyl)quinazoline,
6-dimethylaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6,7-dimethoxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-(3,4-dimethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,
6-dimethylaminomethylideneaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-(phenylmethylaminosulfonyl)-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-(2-phenylethyl)amino-2-(1 -imidazolyl)quinazoline,
4-cyclohexylmethylamino-2-(1 -imidazolyl)quinazoline,
6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-phenylmethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-iodo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-hydroxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-(4-trifuloromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-2-(2-azepinyl)quinazoline,
4-phenylmethylamino-2-(1,5-diazepin-2-yl)quinazoline,
4-phenylmethylamino-2-(2-pyrimidinyl)quinazoline,
4-phenylmethylamino-2-(2-triazinyl)quinazoline,

4-phenylmethylamino-2-(2-pyrrolyl)quinazoline,
4-phenylmethylamino-2-(1-triazolyl)quinazoline,
6-hydroxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-(3-trifluoromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline
4-phenylmethylamino-6,8-diiodo-2-(1-imidazolyl)quinazoline,
4-(2-phenoxyethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
6-hydroxymethyl-4-phenylmethylamino-2-(3-pyridyl)quinazoline
6-methylthio-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
6-methylsulfinyl-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
6-methylsulfinyl-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-2-(2-thienyl)quinazoline,
4-phenylmethylamino-2-(2-furyl)quinazoline,
4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,
6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,
6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,
6-ethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,
4-(2-methoxyethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline or
4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline.

European published application number 0636626, which discloses compounds of the formula



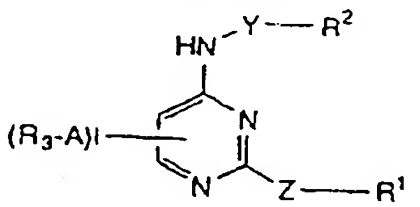
(1)

and salts and solvates (e.g. hydrates) thereof, in which:
R^1 represents arylmethyl or C_{1-6}alkyl optionally substituted by one or more fluorine atoms;
R^2 represents methyl;
R^3 represents C_{2-4}alkyl;
R^4 represents nitro, cyano, C_{1-6}alkoxy, $C(=X)NR^6R^7$, NR^8R^9, $(CH_2)_mNR^{10}C(=Y)R^{11}$ or a 5-membered heterocyclic ring selected from thienyl, thiazolyl and 1,2,4-triazolyl each ring optionally substituted by a C_{1-4}alkyl or aryl group; or when R^1 is arylmethyl or C_{1-6}alkyl substituted by one or more fluorine atoms then R^4 may also represent hydrogen;
R^5 represents hydrogen or C_{1-6}alkyl;
R^6 represents hydrogen or C_{1-6}alkyl;
R^7 represents hydrogen, amino, hydroxyl, C_{1-6}alkyl, aryl or arylC_{1-4}alkyl;
R^8 represents hydrogen or C_{1-6}alkyl;
R^9 represents hydrogen, C_{1-6}alkyl, SO_2R^{12}, CO_2R^{12}, $C(=NCN)SR^{12}$ or $C(=NCN)NR^{13}R^{14}$;
R^{10} represents hydrogen or C_{1-6}alkyl;
R^{11} represents C_{1-6}alkyl optionally substituted by one or more halogen atoms, or R^{11} represents aryl, arylC_{1-4}alkyl, thienyl, $NR^{15}R^{16}$, $CH_2NR^{17}R^{18}$ or R^{10} and R^{11} together represent $-A(CH_2)_n-$;
R^{12} represents C_{1-6}alkyl, aryl or arylC_{1-4}alkyl;
R^{13} represents hydrogen or C_{1-6}alkyl;
R^{14} represents hydrogen, C_{1-6}alkyl, aryl, arylC_{1-4}alkyl or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a morpholine, piperazine or N-C_{1-4}alkylpiperazine ring;
R^{15} represents hydrogen or C_{1-6}alkyl or R^{10} and R^{15} together represent $-A(CH_2)_n-$;
R^{16} represents hydrogen, C_{1-6}alkyl, aryl, arylC_{1-4}alkyl, CO_2R^{12}, $CH_2CO_2R^{12}$ or R^{15} and R^{16} together with the nitrogen atom to which they are attached form a morpholine, piperazine or N-C_{1-4}alkyl-piperazine ring;
R^{17} represents hydrogen or C_{1-6}alkyl;
R^{18} represents hydrogen, C_{1-6}alkyl, aryl, arylC_{1-4}alkyl, COR^{12} or R^{17} and R^{18} together with the nitrogen atom to which they are attached form a morpholine, piperazine or N-C_{1-4}alkylpiperazine ring;
A represents CH_2 or C=O;
m represents zero or 1;
n represents 1,2 or 3;
X represents S or NH, or when R^7 represents amino then X may also represent O;
Y represents O or S; for use in therapy.

Preferred compounds include:

1,3-Dimethyl-6-(2-propoxy-5-acetamidophenyl)-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;
1-ethyl-3-methyl-6-[2-propoxy-5-(4-methyl-2-thiazolyl)phenyl]-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;
1-ethyl-3-methyl-6-[2-propoxy-5-(2-methyl-4-thiazolyl)phenyl]-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;
1-ethyl-3-methyl-6-[2-propoxy-5-(2-(3-pyridyl)-4-thiazolyl)phenyl]-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;
1,3-dimethyl-6-[2-propoxy-5-(2-methyl-4-thiazolyl)phenyl]-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;
1,3-dimethyl-6-[2-propoxy-5-(3-phenyl-1,2,4-triazol-5-yl)phenyl]-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;
1,3-dimethyl-6-(2-propoxy-5-methanesulfonamidophenyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one;
and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

European published application number 0640599, which discloses compounds of the formula



(I)

wherein A is a bond, C1-4 alkylene or C1-4 oxyalkylene;
Y is a bond, C1-4 alkylene, C1-4 alkyleneoxy, C1-4 alkoxyphenylene or phenyl(C1-4)alkylene;
Z is a bond or vinylene;

R1 is 4-15 membered heterocyclic ring containing one or two nitrogen atoms optionally substituted by one or two groups chosen from C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl and nitro;

R2 is (i) 4-15 membered heterocyclic ring containing one or two hetero atoms chosen from nitrogen, oxygen, and sulphur, not more than one hetero atom being sulphur, optionally substituted by one or two groups chosen from C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, nitro and groups of formula:

-COOR10

wherein R10 is hydrogen or C1-4 alkyl,
(ii) C4-15 carbocyclic ring,
(iii) C1-4 alkoxy,
(iv) hydroxy(C1-4 alkoxy) or
(v) hydroxy;

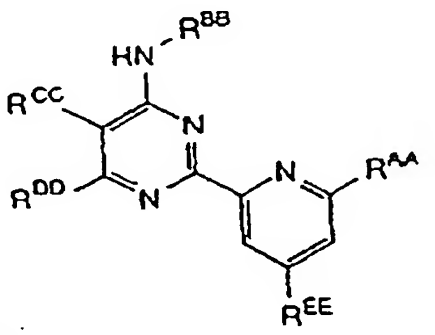
R3 is (i) 4-15 membered heterocyclic ring containing one or two hetero atoms chosen from nitrogen, oxygen and sulphur, not more than one hetero atom being oxgen or sulphur, optionally substituted by one or two groups chosen from C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, nitro, cyano, ethynyl and groups of formula:

-SONR7R8

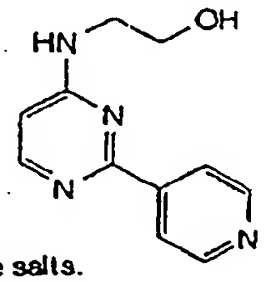
wherein R7 and R8 are independently hydrogen or C1-4 alkyl.
(ii) C4-15 carbocyclic ring,
(iii) a group of formula:

CH2=CH(X)-

wherein X is halogen, or
(iv) hydrogen,
and l is 1 or 2,
provided that: R2 is not hydroxy when Y is a bond; R1 is not bonded through its nitrogen atom when Z is vinylene; and excluding compounds of the formula:



wherein R^{AA} is methyl or n-propyl;
R^{BB} is cyclopentyl, cyclohexyl, 2-hydroxyethyl, methoxyethyl, 2-(1-piperidinyl)ethyl, or phenyl or benzyl which may be substituted by 1 or 2 of methyl, methoxy, chloro, nitro and trifluoromethyl;
R^{CC} is hydrogen or methyl;
R^{DD} is methyl or n-propyl, isopropyl or benzyl; and
R^{EE} is hydrogen or methyl;
and the compound of formula:



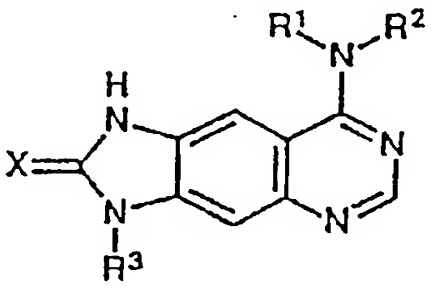
and its pharmaceutically acceptable salts.

Preferred compounds include:

2-(1-Imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-5-(3-methoxyphenyl)-methylpyrimidine,
2-(1-Imidazolyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-4-(2-methoxyethyl)aminopyrimidine,
2-(1-Imidazolyl)-5-ethyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-phenylmethyl-4-phenylmethylaminopyrimidine
2-(1-Imidazolyl)-5-methyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5,6-dimethyl-4-phenylmethylaminopyrimidine

2-(1-Imidazolyl)-5-(3-methoxyphenyl)methyl-4-(2-methoxyethyl)amino-pyrimidine,
2-(1-Imidazolyl)-5-(4-methoxyphenyl)methyl-4-[2-(2-hydroxyethoxy)ethyl]-aminopyrimidine,
2-(1-Imidazolyl)-5-(4-methoxyphenyl)methyl-4-(2-methoxyethyl)amino-pyrimidine,
2-(1-Imidazolyl)-5-(4-methoxyphenyl)methyl-4-phenylmethylamino-pyrimidine,
2-(1-Imidazolyl)-5-phenoxymethyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(1-imidazolyl)methyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(1-chlorovinyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thiazolyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-[2-(2-hydroxyethoxy)ethyl] aminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(1-naphthyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(4-methoxyphenyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-methoxyphenyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-furyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-thienyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-pyridyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-methoxyethyl) aminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-phenylmethoxyaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(4-chlorophenyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-chlorophenyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(4-methylphenyl)-4-(1,3-dioxaindan-5-yl) methylamino-pyrimidine,
2-(1-Imidazolyl)-5-(4-methoxyphenyl)-4-(1,3-dioxaindan-5-yl) methylamino-pyrimidine,
2-(1-Imidazolyl)-5-(5-methyl-2-thienyl)-4-(1,3-dioxaindan-5 -yl)methylamino-pyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-[4-(1-imidazolyl)phenyl] methylamino-pyrimidine,
2-(1-Imidazolyl)-5-(3-pyridyl)-4-(1,3-dioxaindan-5-yl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(3-furyl)-4-(1,3-dioxaindan-5-yl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(3-pyridyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(4-chlorophenyl)-4-(1,3-dioxaindan-5-yl) methylamino-pyrimidine,
2-(Benzimidazol-1-yl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl) methylamino-pyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(4-ethoxycarbonylphenyl) methylamino-pyrimidine,
2-(1-Imidazolyl)-5-(2-naphthyl)-4-(1,3-dioxaindan-5-yl) methylamino-pyrimidine,
2-(3-Pyridyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl) methylaminopyrimidine,
2-[2-(3-Pyridyl)vinyl]-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl) methylamino-pyrimidine,
2-(2-Methyl-1-Imidazolyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl)methylamino-pyrimidine or
2-(1-Imidazolyl)-5-(2-thienyl)-4-(benzimidazol-5-yl) methylaminopyrimidine

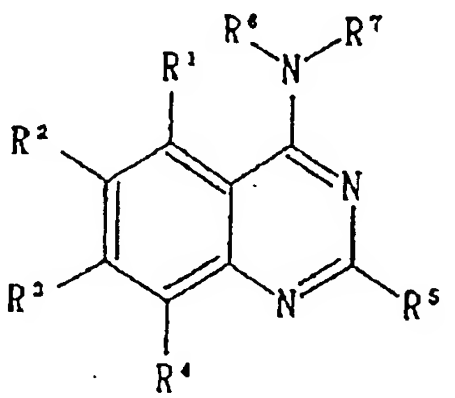
European published application number 0668280, which discloses compounds of the formula



(I)

wherein R^1 and R^2 are the same or different and represent hydrogen, lower alkyl (which is optionally substituted with one to three substituents which are the same or different and are cycloalkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, halogen, alicyclic heterocycle group (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, aralkyl, aryl optionally substituted with one to three substituents which are the same or different and are lower alkoxy, or aromatic heterocycle group)), cycloalkyl, bicycloalkyl, benzocycloalkyl (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen, or trifluoromethyl), lower alkenyl, aryl (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen, or trifluoromethyl), aromatic heterocycle group-substituted alkyl (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen or trifluoromethyl and where said alkyl part is optionally substituted with aryl), aromatic heterocycle group (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen, or trifluoromethyl), or aralkyl (where the aryl part of said aralkyl is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen, or trifluoromethyl), or R^1 and R^2 are taken together to represent heterocycle group containing nitrogen atom (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, aryl, or aralkyl), R^3 represents hydrogen, lower alkyl (which is optionally substituted with one to three substituents which are the same or different and are cycloalkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, halogen, or alicyclic heterocycle group (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, aralkyl, aryl optionally substituted with one to three substituents which are the same or different and are lower alkoxy, or aromatic heterocycle group)), cycloalkyl, lower alkenyl, aryl (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen, or trifluoromethyl), aromatic heterocycle group-substituted alkyl (where said aromatic heterocycle group part is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen or trifluoromethyl, and where the alkyl part is optionally substituted with aryl), aromatic heterocycle group (where said aromatic heterocycle group is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen, or trifluoromethyl), or aralkyl (where the aryl part of said aralkyl is optionally substituted with one to three substituents which are the same or different and are lower alkyl, lower alkoxy, dialkyl-substituted amino, halogen, or trifluoromethyl), and X represents oxygen atom or sulfur atom, or pharmacologically acceptable salts thereof.

European published application number 0669324, which discloses compounds of the formula



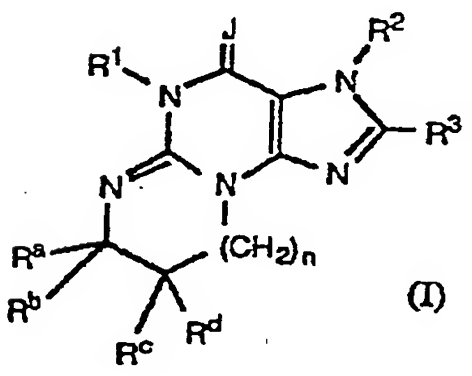
(I)

(wherein R^1, R^2, R^3, R^4 and R^5 may be the same or different from each other and each represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group; and

R^6 and R^7 may be the same or different from each other and each represents a hydrogen atom, a lower alkyl group, a hydroxyalkyl group, a lower alkoxyalkyl group, a cyanoalkyl group, a heteroarylalkyl group, a cycloalkyl group, a cycloalkylalkyl group or a carboxyl alkyl group which may be protected, or alternatively R^6 and R^7 may form a ring together with the nitrogen atom to which they are bonded, this ring optionally having a substituent).

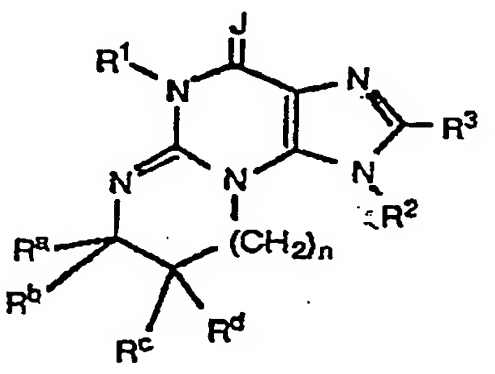
or a pharmacologically acceptable salt thereof:

WO91/19717 discloses compounds of the formula



(I)

and



(I')

wherein

J is oxygen or sulfur,

R^1 is hydrogen, alkyl or alkyl substituted with aryl or hydroxy;

R^2 is hydrogen, aryl, heteroaryl, cycloalkyl, alkyl or alkyl substituted with aryl, heteroaryl, hydroxy, alkoxy, amino, monoalkyl amino or dialkylamino, or $-(CH_2)_mTCOR^{20}$ wherein m is an integer from 1 to 6, T is oxygen or -NH- and R^{20} is hydrogen, aryl, heteroaryl, alkyl or alkyl substituted with aryl or heteroaryl;

R^3 is hydrogen, halo, trifluoromethyl, alkoxy, alkylthio, alkyl, cycloalkyl, aryl, aminosulfonyl, amino, monoalkylamino, dialkylamino, hydroxyalkylamino, aminoalkylamino, carboxy, alkoxycarbonyl or aminocarbonyl or alkyl substituted with aryl, hydroxy, alkoxy, amino, monoalkylamino or dialkylamino;

R^a, R^b, R^c and R^d independently represent hydrogen, alkyl, cycloalkyl or aryl; or (R^a and R^b) or (R^c and R^d) or (R^b and R^c) can complete a saturated ring of 5- to 7- carbon atoms, or (R^a and R^b) taken together and (R^b and R^c) taken together, each complete a saturated ring of 5- to 7-carbon atoms, wherein each ring optionally can contain a sulfur or oxygen atom and whose carbon atoms may be optionally substituted with one or more or the following: alkenyl, alkynyl, hydroxy, carboxy, alkoxycarbonyl, alkyl or alkyl substituted with hydroxy, carboxy or alkoxycarbonyl; or such saturated ring can have two adjacent carbon atoms which are shared with an adjoining aryl ring; and

n is zero or one.

Preferred compounds include:

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(phenylmethyl)-cyclopenta[4,5]imidazo[2,1-b]purin-4-one;

7,8-Dihydro-5-methyl-3-(phenylmethyl)-3*H*-imidazo[2,1-b]purin-4(5*H*)-one;

cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-3-(phenylmethyl)-3*H*-benzimidazo[2,1-b] purin-4(5*H*)-one;

5,7,8,9-Tetrahydro-5-methyl-3-(phenylmethyl)pyrimido[2,1-b]purin-4(3*H*)-one;

7,8-Dihydro-8-phenyl-5-methyl-3-(phenylmethyl)-3*H*-imidazo[2,1-b]purin-4(5*H*)-one;

5',7'-Dihydro-5'-methyl-3'-(phenylmethyl)spiro[cyclohexane-1,8'-(8*H*)-imidazo[2,1-b]purin]-4'(3'*H*)-one;

cis-5,6a,11,11a-Tetrahydro-5-methyl-3-(phenylmethyl)indeno[1',2':4,5]imidazo[2,1-b]purin-4(3*H*)-one;

5',7'-Dihydro-2',5' dimethyl-3'-(phenylmethyl)spiro{cyclohexane-1,7'(8'H)-imidazo[2,1-b]purin}-4'(3'H)-one;

7,8-Dihydro-2,5,7,7,8(R,S)-pentamethyl-3H-imidazo[2,1-b]purin-4(5H)-one;

cis-5,6a,7,11b-Tetrahydro-5-methyl-3-

(phenylmethyl)indeno[2',1':4,5]imidazo[2,1-b]purin-4(3*H*)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4-(3*H*)-one;
5'-Methyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'(8'*H*)-(3'*H*)-imidazo[2,1-b]purin]-4'(5'*H*)-one;
7,8-Dihydro-2,5,7,7-tetramethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5'H)-one;
7,8-Dihydro-7(R)-phenyl-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-3,7(R)-bis(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
(±)-7,8-Dihydro-2,5-dimethyl-7-ethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
6a(S)-7,8,9,10,10a(R)-Hexhydro-2,5-dimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
6a(R)-7,8,9,10,10a(S)-hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R)-isopropyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5,7(R)-trimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
cis-7,7a,8,9,10,10a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H-cyclopenta[5,6]pyrimido[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylpropyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R)-(2-methylpropyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R,S)-(methoxycarbonyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R,S)-(1-propyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylethyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5,7,7,8(R,S)-pentamethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
5,7,8,9-Tetrahydro-2,5,7,9(R,S)-pentamethyl-3-(phenylmethyl)-pyrimido[2,1-b]purin-4(3H)-one;
5,6a(*R*),7,8,9,9a(*S*)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;
5,6a(*S*),7,8,9,9a(*R*)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;

cis-6a,7,8,9,10,10a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-3*H*-benzimidazo[2,1-b]purin-4(5*H*)-one;

5',7'-Dihydro-2',5'-dimethyl-3'-(phenylmethyl)spiro[cyclohexane-1,8'-(8*H*)-imidazo[2,1-b]purin]-4'(3'*H*)-one;

cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-cyclohept[6,7]imidazo[2,1-b]purin-4(3*H*)-one;

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;

cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)-3*H*-benzimidazo[2,1-b]purin-4-(5*H*)-one;

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-phenyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;

cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-2-phenyl-3-(phenylmethyl)-3*H*-benzimidazo[2,1-b]purin-4(5*H*)-one;

cis-5,6a,7,8,9,9a-Hexahydro-5-methylcyclopenta[4,5]imidazo[2,1-b]purin-4(3*H*)-one;

cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethylcyclopenta[4,5]imidazo[2,1-b]-purin-4(3*H*)-one;

cis-5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-di-methyl-cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;

2'-Methyl-3'-spiro{cyclopentane-1,7'(8'H)-(3'H]-imidazo[2,1-b]purin}-4'(5'H)-one;

7,8-Dihydro-2,5-dimethyl-7(R)-(1-methylethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;

7,8-Dihydro-2,5,7,7-tetramethyl-3H-imidazo[2,1-b]purin-4(5H)-one;

7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;

6a(R),7,8,9,10,10a(S)-Hexahydro-2,5-dimethyl-3H-benzimidazo[2,1-b]purin-4(5H)-one;

5',7'-Dihydro-2',5'-dimethylspiro{cyclohexane-1,7'(8'H)-imidazo[2,1-b]purin}-4'(3'H)-one;

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(phenylmethyl)cyclopenta[4,5]imidazo[2,1-b]purin-4(3*H*)-thione;

5,6a(*R*),7,8,9,9a(*S*)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-thione;

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(4-chlorophenyl-methyl)cyclopenta[4,5]imidazo[2,1-b]purin-4(3*H*)-one;

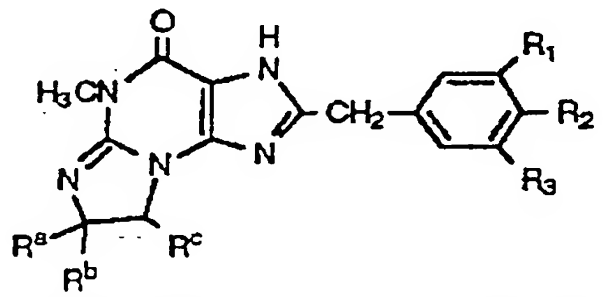
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(cyclohexylmethyl)-

cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(2-naphthylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;
bromophenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R)-7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(4-methoxyphenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2,3,5-trimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2-(hydroxymethyl)-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one;
cis-5,6a,7,8,9,9a-Hexahydro-2-methylthio-5-methyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-3,4,5,6a,7,8,9,9a-Octahydro-5-methyl-4-oxo-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-2-carboxylic acid;
cis-3,4,5,6a,7,8,9,9a-Octahydro-5-methyl-4-oxo-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-2-carboxylic acid, methyl ester;
cis-5,6a,7,8,9,9a-Hexahydro-2-bromo-5-methyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one;
cis-5,6a,7,8,9,9a-Hexahydro-2-(methylaminosulfonyl)-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one;
cis-1-Cyclopentyl-5,6a,7,8,9,9a-hexahydro-5-methyl-cyclopent[4,5]imidazo[2,1-b]purin-4-(1*H*)one;
cis-5,6a,7,8,9,9a-Hexahydro-3,5-bis-(phenylmethyl) cyclopent(4,5)imidazo(2,1-b)purin-4(3*H*)one;
cis-6a,7,8,9,10,10a-Hexahydro-3,5-bis-(phenylmethyl)-3*H*-benzimidazo[2,1-b]purin-4(5*H*)one;
cis-3-Cyclopentyl-5,6a,7,8,9,9a-hexahydro-5-methyl-cyclopent[4,5]imidazo(2,1-b)purin-4(3*H*)one;
5'-Methyl-3'-(phenylmethyl)spiro[cyclopentane-1,7'(8'*H*)-(3'*H*)-imidazo[2,1-b]purin]-4'(5'*H*)one;
2',5'-Dimethyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'(8'*H*)-(3'H)-imidazo[2,1-b]purin]-4'(5'*H*)one;
cis-5,6a,(R)7,8,9,9a(S)-Hexahydro-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo(2,1-b)purin-4(3*H*)one;
cis-3-Cyclopentyl-5,6a,7,8,9,9a-Hexahydro-2,5-dimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)one;36
5'-Methyl-2'-trifluoromethyl-3'-(phenylmethyl)spiro{cyclo-pentane-1,7'(8'*H*)-(3'*H*)imidazo[2,1-b]purin}-4'(5'*H*)-one;
7,8-Dihydro-5,7,7-trimethyl-2-trifluoromethyl-3-(phenylmethyl)-3*H*-imidazo[2,1-b]purin-4(5H)-one;

(+/-)-cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-trifluoromethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
(+/-)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-(phenylmethyl)-3H-pentaleno[6a',1':4,5] imidazo[2,1-b] purin-4(5H)-one;
(+)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-phenylmethyl-3H-pentaleno[6a',1':4,5] imidazo[2,1-b] purin-4(5H)-one;
(-)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-phenylmethyl-3H-pentaleno[6a',1':4,5] Imidazo[2,1-b] purin-4(5H)-one;
(+/-) 6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5] imidazo[2,1-b] purin-4(5H)-one;.
(+)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5] imidazo[2,1-b] purin-4(5H)-one;
(-)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5] imidazo[2,1-b] purin-4(5H)-one;
6a,7,8,9,10,10a,11,12,13,13a-Decahydro-2,5-dimethyl-(3-phenylmethyl)napth[1,8a-d]imidazo[2,1-b]purin-4(5H)one;
7(R)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(3H)-one;
7(R)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
7(S)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(3H)-one;
7(S)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[(trimethylacetoxy)methyl]-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(4-pyridylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[2-(1-morpholinyl)ethyl]cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[acetoxymethyl]cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a,7,8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(*R*),7(*S*),8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(*S*),7(*R*),8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one];
cis-6a,7,8,9,10,10a-Hexahydro-2,5,7-trimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one];

cis-5,6a,7,8,9,9a-Hexahydro-2,5,6a-trimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one]; or
cis-6a,7,8,9,10,10a-Hexahydro-2,5,7-trimethyl-3H-benzimidazo[2,1-b]purin-4(5H)-one].

WO 94/19351 discloses compounds of the formula



or a pharmaceutically acceptable salt thereof, wherein:

R_1, R_2 and R_3 are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, halogeno, hydroxy, (di-lower alkyl)amino, 4-morpholinyl, 1-pyrrolidinyl, 1-pyrrolyl, $-CF_3$, $-OCF_3$, phenyl and methoxyphenyl; or R_1 and R_2 together are methylenedioxy; or R_1 and R_2 together with the carbon atoms to which they are attached form a benzene ring; and

R^a is hydrogen and R^b and R^c, together with the carbon atoms to which they are attached, form a saturated ring of 5 carbons; or R^a is lower alkyl, R^b is hydrogen or lower alkyl, and R^c is hydrogen; or R^a, R^b and the carbon atom to which they are attached form a saturated ring of 5-7 carbons, and R^c is hydrogen; or R^a is hydrogen, and R^b, R^c and the carbon atoms to which they are attached form a tetrahydrofuran ring; or R^a and R^b, together with the carbon atom to which they are attached, and R^b and R^c, together with the carbon atoms to which they are attached, each form a saturated ring of 5-7 carbons.

Preferred compounds include:

2'-benzyl-spiro[cyclopentane-1',7' (8'H)-[3'H]-imidazo[2,1-b]purin-4'-(5'H)-one;

2'-benzyl-5,7,7-trimethyl-3H-imidazo[2,1-b]purin-4-(5H)-one;

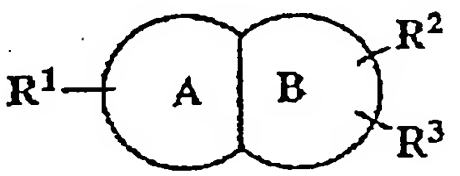
(+)-2-benzyl-7, 8-dihydro-5-methyl-7-(1-methylethyl)-1H-imidazo[2,1-b]-purin-4(5H)-one;

(+,-)-6a, 7, 8, 9, 9a, 10, 11, 11a-octahydro-5-methyl-2-(3,4-methylene-dioxyphenylmethyl)-3H-pentalen[6a,1:4,5]imidazo[2,1-b]purin-4(5H)-one; and

(+)-cis-6a, 7, 9, 9a-tetrahydro-5-methyl-2-[4-(trifluoromethyl)-phenylmethyl]-3H-furo[3', 4':4,5]imidazo[2,1-b]purin-4(5H)-one.

WO 94/22855 discloses compounds of the formula

1. A nitrogen-containing fused-heterocyclic compound having the formula (I) or a pharmacologically acceptable salt thereof:



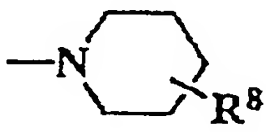
(I)

in which ring A represents a benzene, pyridine or cyclohexane ring and B represents a pyridine, imidazole or pyrimidine ring, with the proviso that rings A and B are bonded to each other with two atoms being shared by them, and the shared atoms may be any of carbon and nitrogen atoms;

R^1 represents a group represented by the formula: $-NR^4R^5$ (wherein R^4 and R^5 may be the same or different

from each other and each represent a hydrogen atom, a lower alkyl or acyl group or a carboxyl group which may be protected, or alternatively R^4 and R^5 may form a ring together with the nitrogen atom to which they are bonded, provided that the ring may be substituted), or a heteroaryl group which has one or two nitrogen atoms and may be substituted;

R^2 represents a hydrogen atom, a group represented by the formula:

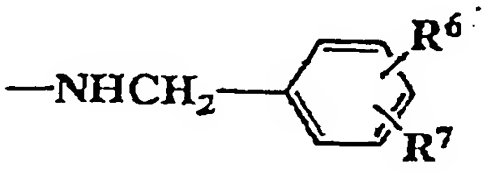


(wherein R^8 represents a carboxyl or tetrazolyl group which may be protected),

or a halogen atom;

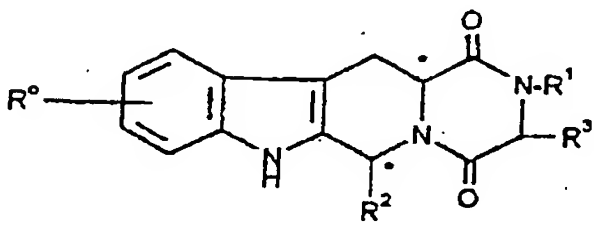
and

R^3 represents a hydrogen atom or a group represented by the formula:



(wherein R^6 and R^7 each represent a hydrogen or halogen atom or a lower alkoxy group, or alternatively R^6 and R^7 may together form a methylenedioxy or ethylenedioxy group).

WO 95/19978 discloses compounds of the formula



(I)

and salts and solvates thereof, in which:

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring  attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

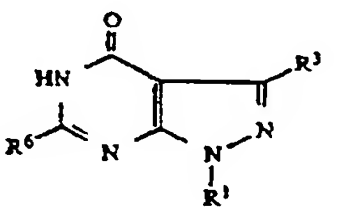
R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain.

Preferred compounds include:

Cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2', 1' : 6,1]pyrido[3,4-b]indole-1,4-dione;
Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;
(6R, 12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2', 1' : 6,1] pyrido [3,4-b] indole-1,4-dione;
(5aR, 12R, 14aS)-1,2,3,5,6,11,12,14a-Octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo[1",2" : 4',5']pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-5-1,4-dione;
and physiologically acceptable salts and solvates thereof.

U.S. Patent No. 5,294,612 discloses compounds of the formula



wherein:

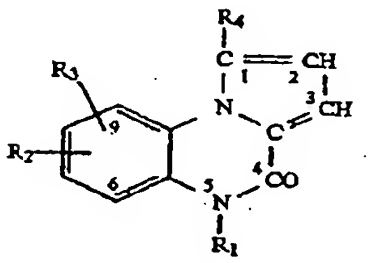
R^1 is hydrogen, alkyl, C_4 to C_7 cycloalkyl, C_4 to C_7 cycloalkyl substituted by C_1 to C_{10} alkyl or hydroxyl, 2- or 3-tetrahydrofuranyl, 3-tetrahydrothienyl 1,1, -dioxide, C_4 to C_7 cycloalkyl-C_1 to C_{10} alkyl, carboxy-C_1 to C_{10} alkyl, carbo-C_1 to C_4 lower-alkoxy-C_1 to C_{10} alkyl, dialkylamino C_1 to C_{10} alkyl, phenyl-C_1 to C_4 lower-alkyl, phenyl-C_1 to C_4 lower-alkyl in which the phenyl ring is substituted in the 2, 3, or 4-position by one or two substituents, the same or different, selected from the group consisting of amino, halogen, C_1 to C_{10} alkyl, carboxyl, carbo-C_1 to C_4 lower-alkoxy, carbamoyl, $NHSO_2$-(quinolinyl), nitro and cyano;

R^3 is, C_1 to C_4 lower-alkyl, phenyl-C_1 to C_4 lower-alkyl, lower-alkoxyphenyl-C_1 to C_4 lower-alkyl, diC_1 to C_4 lower-alkoxy-phenyl-C_1 to C_4 lower-alkyl, pyridyl-C_1 to C_4 lower-alkyl, C_4 to C_7 cycloalkyl-C_1 to C_4 lower-alkyl, phenylamino, diC_1 to C_{10} alkylamino, halogen, trifluoromethyl, C_1 to C_4 lower-alkylthio, cyano or nitro; and

R^6 is a nine or ten membered bicyclic ring having carbon and from one to two nitrogen atoms, and

the heterocycle is made up of fused 5 or 6 membered rings or such ring substituted at any available carbon atom by one or two substituents, the same or different, selected from the group consisting of C_1 to C_4 lower-alkyl, halogen, C_1 to C_4 lower-alkoxy, C_4 to C_7 cycloalkyloxy, 4-morpholinyl, C_1 to C_4 lower-alkoxy-C_1 to C_4 lower-alkoxy, hydroxy, imidazolyl, oxo and 4-morpholinyl-C_1 to C_4 lower-alkoxy, or at any available nitrogen atom by C_1 to C_4 lower-alkyl, C_2 to C_4 lower-alkanoyl, or trifluoroacetyl; or a pharmaceutically acceptable acid-addition salt thereof.

U.S. Patent No. 5,405,847 discloses compounds of the formula



I

where the benzo ring can also contain a nitrogen atom instead of a CH group either in position 6, 7, 8 or 9 and the radicals R_1, R_2, R_3 and R_4 have the following meanings:

R_1: C_2–C_6-alkenyl, C_2–C_6-alkynyl, hydroxy, C_1–C_6-alkoxy, C_3–C_6-alkenyloxy, C_3–C_6-alkynyloxy, C_2–C_6-alkanoyloxy, benzoyloxy, morpholinocarbonyloxy, C_1–C_6-alkyloxycarbonyloxy, C_1–C_6-alkylaminocarbonyloxy, C_1–C_6-dialkylaminocarbonyloxy or the group

-Alk-A

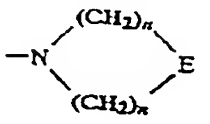
where Alk is C_1–C_6-alkyl, C_2–C_6-hydroxyalkyl or C_3–C_6-cycloalkyl and the symbol A represents:

1) Hydrogen, halogen, hydroxy, C_1–C_6-alkoxy, C_2–C_6-alkanoyloxy, phenyl;
2) —NHR$_5$, —NR$_5$R$_6$, NR$_5$R$_6$R$_7$, pyridylamino, imidazolyl, pyrrolidinyl, N—C_1–C_6-alkylpyrrolidinyl, piperidylamino, N-(phenyl-C_1–C_4-alkyl)-piperidylamino where R_5 and R_6 may be the same or different and represent hydrogen, C_1–C_6-alkyl, C_3–C_7-cycloalkyl, C_3–C_7-hydroxycycloalkyl, morpholino-C_1–C_6-alkyl, phenyl, phenyl-C_1–C_6-alkyl or phenyl-C_2–C_6-oxyalkyl, it also being possible for the phenyl radicals in R_5 and R_6 to be substituted by halogen and R_7 is hydrogen or C_1–C_6-alkyl;
3) The group:

-CO-D

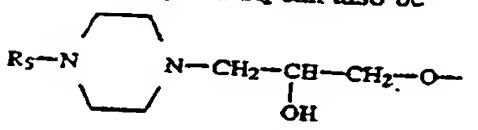
where D is phenyl, C_1–C_6-alkyl, C_3–C_7-cycloalkyl, hydroxy, C_1–C_6-alkoxy, C_3–C_7-cycloalkyloxy, morpholino, pyrrolidino, piperidino, homopiperidino, piperazino, —NHR$_5$ or —NR$_5$R$_6$ and R_5 and R_6 have the meanings given hereinabove;

4) The group:

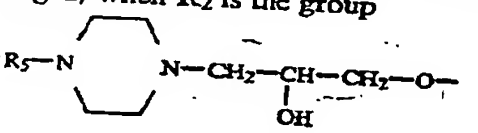


where n can be the integers 1-3 and E represents CH_2, oxygen, sulfur, NH, CHOH, CH—C_1–C_6-alkyloxy, CH—C_2–C_6-alkanoyloxy, CHC_6H_5, CHCOD, CH—$CH_2C_6H_5$, N—C_1–C_6-alkyl, N—C_1–C_6-hydroxyalkyl, N—C_6H_5, N—$CH_2C_6H_5$, N—$CH(C_6H_5)_2$, N—$(CH_2)_2$—OH, N—$(CH_2)_3$—OH or NCOD and the phenyl radicals (C_6H_5) may also be substituted by halogen, C_1–C_6-alkoxy, trifluoromethyl, C_1–C_6-alkyl, methylenedioxy or cyan and D has the meanings given hereinabove;

R_2 and R_3, which may be the same or different: hydrogen, halogen, hydroxy, C_1–C_6-alkyl, trifluoromethyl, —CN, C_1–C_6-alkoxy, C_3–C_6-alkenyloxy, C_3–C_6-alkynyloxy, —NHR_5, —NR_5R_6, $NR_5R_6R_7$ (meanings R_5, R_6, R_7 as given hereinabove) or the group -G-Alk-A, where Alk and A have the meanings given hereinabove and G is oxygen, sulfur, NH or NR_5 and R_2 can also be

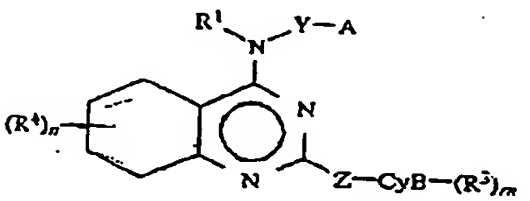


R_4: hydrogen or halogen, where R_1 can also be hydrogen, when R_2 is the group



and R_5 represents phenyl, C_1–C_4-alkoxyphenyl or diphenylmethyl and R_3 and R_4 are hydrogen, and their physiologically acceptable acid addition salts and quaternary ammonium salts, with the exception of the compounds of Formula I where R_1 is methyl, dimethylaminopropyl, dimethylaminoethyl, morpholinoethyl or pyrrolidinoethyl, R_2, R_3 and R_4 are hydrogen and the benzo ring does not contain a nitrogen atom instead of a CH group.

U.S. Patent No. 5,436,233 discloses compounds of the formula



(I)

wherein R^1 is hydrogen or C1–4 alkyl;
Y is single bond or C1–6 alkylene;
A is
(i) —CyA—$(R^2)_l$,
(ii) —O—R^0 or —$S(O)_p$—R^0,
in which R^0 is R^{0A} or R^{0B};
R^{0A} is —CyA—$(R^2)l$;
R^{0B} is hydrogen or C1–4 alkyl;
p is 0–2;
CyA is
(1) 3–7 membered, saturated or unsaturated, monocyclic carbocyclic ring,

(2) 7-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one nitrogen atom, one nitrogen and one oxygen atoms, two nitrogen and one oxygen atoms, or one nitrogen and two oxygen atoms,
(3) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one nitrogen and one oxygen atoms, two nitrogen and one oxygen atoms, or one nitrogen and two oxygen atoms,
(4) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as a hetero atom, one nitrogen atom,
(5) 4- or 5-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one nitrogen atom, one nitrogen and one oxygen atoms, two nitrogen and one oxygen atoms, or one nitrogen and two oxygen atoms,
(6) 4–7 membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one or two sulfur atoms or
(7) 4–7 membered, unsaturated or partially or fully saturated, monocyclic hetero ring containing as hetero atoms, one or two oxygen atom;

R^2 is R^{2A} or R^{2B};

R^{2A} is (1) $-NR^6AR^{7A}$, in which R^{6A} and R^{7A} independently are hydrogen or C1–4 alkyl (with the proviso that R^{6A} and R^{7A} are not hydrogen at same time), (2) $-SO_2NR^6R^7$, in which R^6 and R^7 independently are hydrogen or C1–4 alkyl, (3) trifluoromethyl or (4) trifluoromethoxy;

R^{2B} is (1) hydrogen, (2) C1–4 alkyl, (3) C1–4 alkoxy, (4) $-COOR^5$, in which R^5 is hydrogen or C1–4 alkyl, (5) halogen, (6) nitro or (7) $-NRGBR^{7B}$, in which R^{6B} and R^{7B} are hydrogen;

Z is Z^A or Z^B;

Z^A is methylene, ethylene, vinylene or ethynylene;

Z^B is single bond;

CyB is

(1) 7-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one, two or three nitrogen atoms,
(2) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, two or three nitrogen atoms,
(3) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as a hetero atom, one nitrogen atom,
(4) 4- or 5-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one, two or three nitrogen atoms, or
(5) 4–7 membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one or two oxygen atoms, or one or two sulfur atoms;

R^3 is hydrogen, C1–4 alkyl, C1–4 alkoxy, halogen or trifluoromethyl;

R^4 is R^{4A} or R^{4B};

R^{4A} is (1) $-NHSO_2R^{11}$, in which R^{11} is C1–4 alkyl, (2) $SO_2NR^9R^{10}$, in which

R^9 is hydrogen, C1–4 alkyl or phenyl(C1–4 alkyl) and R^{10} is hydrogen or C1–4 alkyl, (3) $-OCOR^{11}$, in which R^{11} is as hereinbefore defined, (4) hydroxy, (5) $-SO_2N{=}CHNR^{12}R^{13}$ in which R^{12} is hydrogen or C1–4 alkyl and R^{13} is C1–4 alkyl, (6) $-CONR^{14}R^{15}$ in which R^{14} is hydrogen or C1–4 alkyl and R^{15} is C1–4 alkyl or phenyl(C1–4 alkyl), (7) ethynyl, (8) tri(C1–4 alkyl)silylethynyl or (9) acetyl;

R^{4B} is (1) hydrogen, (2) C1–4 alkyl, (3) C1–4 alkoxy, (4) —$COOR^8$, in which R^8 is hydrogen or C1–4 alkyl, (5) —NR^9R^{10}, in which R^9 and R^{10} are as hereinbefore defined, (6) —$NHCOR^{11}$, in which R^{11} is as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro, (10) cyano, (11) C1–4 alkylthio, (12) C1–4 alkylsulfinyl, (13) C1–4 alkylsulfonyl, (14) hydroxymethyl, and l, m and n independently are 1 or 2; with the proviso that

(1) the group of the formula: —CyA—$(R^2)_l$ does not represent a cyclopentyl and trifluoromethylphenyl group when Y is a single bond, that

(2) a CyB ring does not bond to Z through a nitrogen atom in the CyB ring when Z is vinylene or ethynylene, that

(3) a CyB ring is not pyridine or thiophene when CyA is a ring of CyA—(7) that

(4) Y is not a single bond, when A is (ii) —O—R^0 or —$S(O)_p$—R^0 and that

(5) A is not —CyA—$(R^2B)l$ and —OR^{0B}, when Z is Z^B and R^4 is R^{4B}; or pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof.

Preferred compounds include:

4-phenylmethylamino-2-((1-imidazolyl)methyl)-quinazoline,

4-phenylmethylamino-2-((1-imidazolyl)methyl)-quinazoline,

6-chloro-4-phenylmethylamino-2-(1-imidazolylmethyl)quinazoline,

6-chloro-4-phenylamino-2-(1-imidazolylmethyl)-quinazoline,

6-chloro-4-(3-carboxyphenyl)amino-2-(1-imidazolylmethyl)quinazoline

or

4-phenylmethylamino-2-(2-(3-pyridyl)vinyl)quinazoline,

and pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof.

6-dimethylaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,

6-dimethylaminomethylideneaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,

6-(phenylmethylaminosulfonyl)-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,

6-phenylmethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,

6-ethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,

6-hydroxy-4-phenylmethylamino-2-(1-imidazolyl)-quinazoline,

6-(1-i midazolyl)-4-(2-methoxyethyl)amino-6-(2-triethylsilylethynyl)quinazoline,

6-ethynyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl)-quinazoline,

6-(1-imidazolyl)-4-phenylmethylamino-6-ethynylquinazoline or

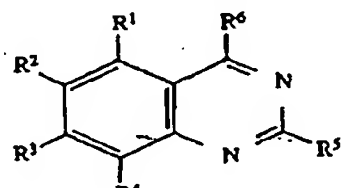
6-acetyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl)-quinazoline,

and pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof.

4-(2-methylthioethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,

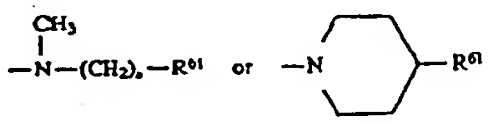
4-(2-methylsulfinylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(2-methylsulfonylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(4-(N,N-dimethylamino)phenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(4-sulfamoylphenylmethyl)amino-2-(3-pyridyl)-quinazoline,
4-(4-trifuloromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,
4-(3-trifluoromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,
4-(2-phenoxyethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline or
4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,
and pharmaceutically acceptable acid addition salts

U.S. Patent No. 5,576,322 discloses compounds of the formula

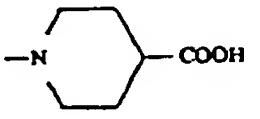


(I)

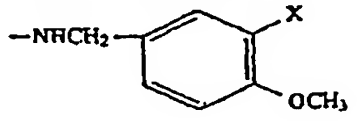
wherein R1, R3, and R4, each of which may be the same or different from each other, may each represent a hydrogen atom, a halogen atom or a lower alkyl group or a lower alkoxy hydrogen atom, R2 is a halogen or cyan group R5 is a group represented by the formula:



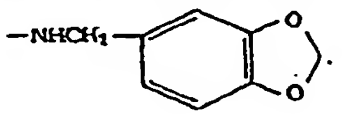
wherein u is 3 or 4 and R61 represents a carboxyl group which may be protected or a heteroaryl group; or R5 is a group represented by the formula:



and R6 is a group represented by the formula



wherein X is hydrogen atom or a halogen atom or



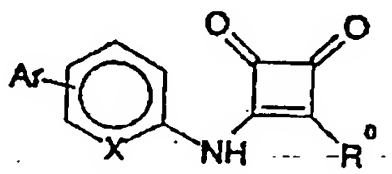
or the pharmacologically acceptable salt thereof.

Preferred compounds include:

2-(4-carboxypiperidino)-4-(3,4-methylene-dioxybenzyl) amino-6-chloroquinazoline- or a pharmaceutically acceptable salt thereof.

Sodium 2-(4-carboxypiperidino)-4-(3,4-methylene-dioxybenzyl) amino-6-chloroquinazoline.

WO 94/29277 discloses compounds of the formula



Formula (1)

or a pharmaceutically acceptable salt thereof, wherein

Ar is an optionally substituted aryl or heteroaryl ring selected from phenyl, naphthyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, imidazolyl, thienyl, oxazolyl, benzimidazolyl, benzoxazolyl, indolyl or thianaphthenyl,

X is CH or N;

R^0 is NR^1R^2 or hydrogen; and

R^1 and R^2 are independently hydrogen or C_{1-6}alkyl.

Preferred compounds include:

3-amino-4-[4-(3-pyridyl)]anilino-3-cyclobutene-1,2-dione,

3-amino-4-[3-(4-imidazolyl)anilino]-3-cyclobutene-1,2-dione,

3-methylamino-4-[3-(5-methyl-4-imidazolyl)anilino]-3-cyclobutene-1,2-dione,

3-dimethylamino-4-[3-(5-methyl-4-imidazolyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(3-methyl-4-pyridyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-oxazolyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(4-pyridyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(3-pyridyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-pyridyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-thienyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(3-thienyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-thianaphthenyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(5-pyrimidyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-benzoxazoyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-benzimidazolyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-indolyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-(3-phenyl)anilino-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-hydroxyphenyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-methoxyphenyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(3-hydroxy-2-pyridyl)anilino]-3-cyclobutene-1,2-dione,

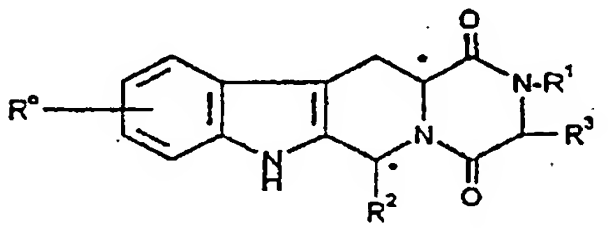
3-amino-4-[3-(2-imidazolyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[6-(4-pyridyl)-2-pyridylamino]-3-cyclobutene-1,2-dione, or

3-[3-(4-pyridyl)anilino]-3-cyclobutene-1,2-dione,

or a pharmaceutically acceptable salt thereof.

WO 95/19978 discloses compounds of the formula

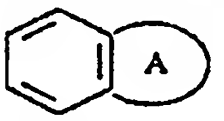


(I)

and salts and solvates thereof, in which:

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

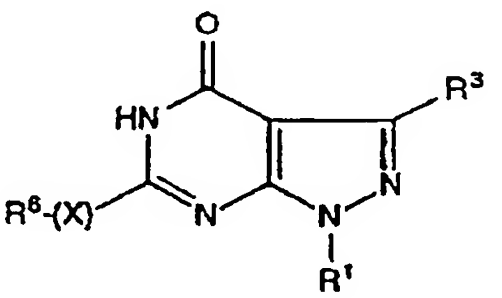
R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring  attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain.

Preferred compounds include:

Cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2', 1' : 6,1]pyrido[3,4-b]indole-1,4-dione;
Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;
(6R, 12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2', 1' : 6,1] pyrido [3,4-b] indole-1,4-dione;
(5aR, 12R, 14aS)-1,2,3,5,6,11,12,14a-Octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo[1",2" : 4',5']pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-5-1,4-dione;
and physiologically acceptable salts and solvates thereof.

WO 96/28429 discloses compounds of the formula



wherein:

R^1 is tert-butyl, or cyclopentyl;

R^3 is methyl, ethyl, or phenylmethyl;

X is $-CH_2-$, -O-, or -NH-; and

R^6 is phenyl (or phenyl substituted by from one to three, the same or different, substituents selected from the group

consisting of lower-alkoxy, hydroxy, halogen, carboxylower-alkoxy, 4-morpholinyl-lower-alkoxy, 5-tetrazolyl-lower-alkoxy, dilower-alkylamino, trifluoromethyl, nitro, amino, lower-alkylsulfonylamino, dilower-alkylamino-lower-alkylphenyl carbonyloxy, and 1-imidazolyl); or when X is $-CH_2-$ R^6 is additionally 2-,3-, or 4-pyridinyl, 1-pyrrolyl, 1-benzimidazolyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 1,2,3,4-tetrahydro-1-quinolinyl, hydroxy, 1-imidazolyl, 1-lower-alkyl-2,3,4, or 5-pyrrolyl, 1-pyrazolyl, 3-,4-, or 5-isoxazolyl(or 3,4, or 5-isoxazolyl substituted on any available carbon atom thereof by lower-alkyl), 2-thienyl, or 3-thienyl; or a pharmaceutically acceptable acid-addition salt and/or hydrate thereof.

Preferred compounds include:

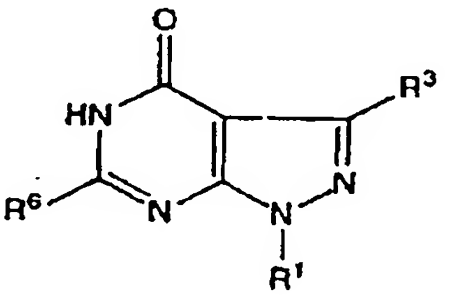
1-cyclopentyl-3-ethyl-6-(4-methoxyphenylmethyl)pyrazolo [3,4-d]pyrimindin-4-one,

1-cyclopentyl-3-ethyl-6-(4-hydroxyphenylmethyl)pyrazolo [3,4-d]pyrimindin-4-one,

1-cyclopentyl-3-ethyl-6-(phenylmethyl)pyrazolo[3,4-d] pyrimindin-4-one, and

1-cyclopentyl-3-ethyl-6-(4-aminophenylmethyl)pyrazolo [3,4-d]pyrimindin-4-one.

WO 96/28448 discloses compounds of the formula



wherein:

R^1 is tert-butyl, or cyclopentyl;

R^3 is lower-alkyl, or phenyl-lower-alkyl; and

R^6 is phenyl, or phenyl substituted by from one to three, the same or different, substituents selected from the group consisting of lower-alkoxy, lower-alkyl, hydroxy, 1-imidazolyl,

lower-alkenyloxy, dilower-alkylamino-lower-alkoxy, 4-morpholinyl-lower-alkoxy, lower-alkoxycarbonyl-lower-alkoxy, carboxylower-alkoxy, trifluoromethyl, 1-piperidinyl-lower-alkoxy, 1-pyrrolidinyl-lower-alkoxy, nitro, halo, amino, -$(CH_2)_2O$-, lower-alkylsulfonylamino, lower-alkoxy-lower-alkoxy, lower-alkenyl, dilower-alkylamino, -$OCH(CH_3)CH_2$-, 4-morpholinylcarbonyl-lower-alkoxy, 4-thiomorpholinyl-lower-alkoxy, pyridinyl-lower-alkoxy, 1-lower-alkyl-3-hexahydroazepinyloxy, and 1-lower-alkyl-4-piperidinyl oxy; or a pharmaceutically acceptable acid-addition salt and/or hydrate thereof.

Preferred compounds include:

1- cyclopentyl-3-ethyl-6-(2-propoxyphenyl)pyrazolo[3,4-d] pyrimindin-4-one,

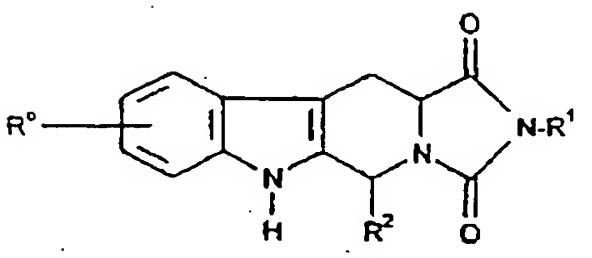
1-cyclopentyl-3-ethyl-6-[4-(1-imidazolyl)phenyl]pyrazolo [3,4-d]pyrimindin-4-one,

1-cyclopentyl-3-ethyl-6-[3-(2-(4-morpholinyl)ethoxy) phenyl]pyrazolo[3,4-d]pyrimindin-4-one,

1-cyclopentyl-3-ethyl-6-[2-ethoxy-4-(1-imidazolyl)phenyl] pyrazolo[3,4-d]pyrimindin-4-one, and

1-cyclopentyl-3-ethyl-6-[2-(CH_2=$CHCH_2O$)phenyl]pyrazolo [3,4-d] pyrimindin-4-one.

WO 96/32003 discloses compounds of the formula



(I)

and salts and solvates thereof, in which:

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 is selected from the group consisting of:

(a) hydrogen;

(b) C_{1-6}alkyl optionally substituted by one or more substituents selected from phenyl, halogen, $-CO_2R^a$ and $-NR^aR^b$;

(c) C_{3-6}cycloalkyl;

(d) phenyl; and

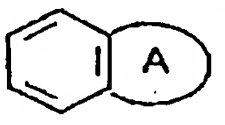
(e) a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from oxygen, nitrogen and sulphur, and being optionally substituted by one or more C_{1-6}alkyl, and optionally linked to the nitrogen atom to which R^1 is attached via C_{1-6}alkyl;

R^2 is selected from the group consisting of:

(f) C_{3-6}cycloalkyl;

(g) phenyl optionally substituted by one or more substituents selected from $-OR^a$, $-NR^aR^b$, halogen, hydroxy, trifluoromethyl, cyano and nitro;

(h) a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from oxygen, nitrogen and sulphur; and

(i) a bicyclic ring 

attached to the rest of the molecule via one of the benzene ring carbon atoms and A is a 5- or 6-membered heterocyclic ring as defined in point (h); and

R^a and R^b independently represent hydrogen or C_{1-6}alkyl.

Preferred compounds include:

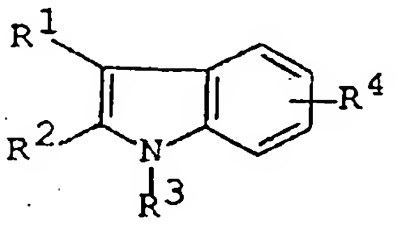
Cis-2-benzyl-5-(3,4-methylenedioxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-benzyl-5-(3,4-methylenedioxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-5-(4-methoxyphenyl)-2-methyl-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-ethyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-ethyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-ethyl-5-(3,4-methylenedioxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-ethyl-5-(2-thienyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-5-(4-dimethylaminophenyl)-2-ethyl-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-9-methyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-9-bromo-2-butyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-9-fluoro-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-9-fluoro-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(3,4-methylenedioxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-5-(3-chlorophenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(3-chlorophenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;

Cis-2-butyl-5-(4-chlorophenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(4-chlorophenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(4-fluorophenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;

Trans-2-butyl-5-(4-hydroxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-5-(4-trifluoromethylphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-5-(4-cyanophenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(4-cyanophenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-5-(4-nitrophenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(4-nitrophenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-5-(3-pyridyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido [3,4-b] indole-1,3(2H)-dione;
Cis-2-butyl-5-(3-thienyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(3-thienyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-5-(3-furyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(3-furyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-cyclohexyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-cyclohexyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-cyclohexyl-9-fluoro-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-cyclohexyl-9-fluoro-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-benzyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido [3,4-b]indole-1,3(2H)-dione;
Cis-2-benzyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-benzyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
(5R,11aR)-2-benzyl-5-(3,4-methylenedioxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-benzyl-5-(4-hydroxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;

Trans-2-(2-chloroethyl)-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-benzyl-5-cyclohexyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-benzyl-5-cyclohexyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-cyclohexyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Cis-2-cyclohexyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-ethoxycarbonylmethyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-5-(4-methoxyphenyl)-2-[2-(2-pyridyl)-ethyl]-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-cyclopropyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans -2-phenethyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-5-phenyl-2-(2-pyridylmethyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-5-phenyl-2-(4-pyridylmethyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-5-(4-methoxyphenyl)-2-(3-pyridylmethyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-(2-dimethylamino-ethyl)-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-(3-dimethylamino-propyl)-5-(4-methoxyphenyl)- 5,6,11,11a-tetrahydro -1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-(2-morpholin-4-yl-ethyl)-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-5-(4-methoxyphenyl)-2-[3-(4-methyl-piperazin-1-yl)-propyl]- 5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-5-(4-methoxyphenyl)-2-(2-pyrrolidin-1-yl-ethyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dion;
Trans-5-(4-methoxyphenyl)-2-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-5,6,11,11a-tetrahydro -1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3 (2H)-dione;
Cis-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3 (2H)-dione;
and pharmaceutically acceptable salts and solvates thereof.

WO 96/32379 discloses compounds of the formula



(I)

wherein

R^1 is hydrogen, halogen, nitro, carboxy, protected carboxy, acyl, cyano, hydroxyimino(lower)alkyl, lower alkenyl optionally substituted with oxo, or lower alkyl optionally substituted with protected carboxy, carboxy or hydroxy;

R^2 is hydrogen, halogen, lower alkenyl, acyl, or lower alkyl optionally substituted with protected carboxy, carboxy, lower alkoxy or hydroxy;

R^3 is lower alkenyl or lower alkyl, both of which are optionally substituted with one or more substituent(s) selected from the group consisting of

(1) oxo,

(2) aryl optionally substituted with one or more substituent(s) selected from the group consisting of halogen, aryl, lower alkoxy, lower alkylenedioxy, cyano, nitro, carboxy, protected carboxy, acyl, and amino optionally substituted with acyl or protected carboxy, and

(3) a heterocyclic group optionally substituted with halogen; and

R^4 is carboxy, protected carboxy, acyl, cyano, halogen, a heterocyclic group, amino optionally substituted with acyl or protected carboxy, or lower alkyl

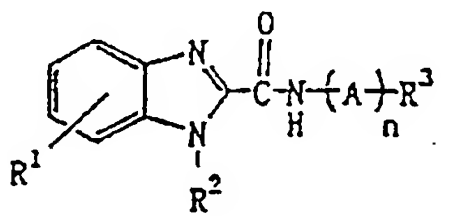
optionally substituted with protected carboxy, carboxy or acyl;

in addition to their significances above,

R^1 and R^2, together with the carbon atoms to which they are attached, represent a 4- to 7-membered carbocyclic ring optionally substituted with oxo,

or its pharmaceutically acceptable salt.

WO 97/03070 discloses compounds of the formula



wherein R^1 is a hydrogen atom or a halogen atom;

R^2 is a phenyl-lower alkyl group;

R^3 is a heterocyclic group selected from the group consisting of an indolyl group, indolinyl group, 1H-indazolyl group, 2(1H)-quinolinonyl group, 3,4-dihydro-2(1H)-quinolinonyl group and 3,4-dihydro-1,4(2H)-benzoxazinyl group, said heterocyclic group may have 1 to 3 substituents selected from the group consisting of:

a group of the formula -B-R^4, (B is a lower alkylene group; R^4 is a 5- to 11-membered saturated or unsaturated heterocyclic group of single ring or binary ring, having 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, oxygen atom and sulfur atom, (said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a lower alkoxy group and

oxo group) or a group of the formula $-NR^5R^6$ (R^5 and R^6 are each the same or different, and a hydrogen atom, a lower alkyl group, a cycloalkyl group, a pyridyl-carbonyl group, an isoxazolylcarbonyl group which may have 1 to 3 lower alkyl groups as the substituents, a pyrrolylcarbonyl group or an amino-substituted lower alkyl group which may have a lower alkyl group as the substituent; further R^5 and R^6 may form 5- to 6-membered saturated heterocyclic group by combining to each other, together with the adjacent nitrogen atom being bonded thereto, further with or without other nitrogen atom or oxygen atom; said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a hydroxy group and a phenyl group)); a lower alkenyl group; a lower alkoxycarbonyl group; a phenoxy-lower alkyl group which may have cyano group as the substituents; a halogen-substituted lower alkyl group; and a lower alkoxycarbonyl-substituted lower alkyl group;

A is a lower alkylene group; and

n is 0 or 1.

Preferred compounds include:

1-Benzyl-6-chloro-2-{1-[3-(imidazol-1-yl)propyl]indol-5-ylaminocarbonyl}benzimidazole.

1-Benzyl-6-chloro-2-{1-[3-(N-cyclohexyl-N-methylamino)propyl]indol-5-ylaminocarbonyl}-benzimidazole.

1-Benzyl-6-chloro-2-{1-[3-(pyrazol-1-yl)propyl]indol-5-ylaminocarbonyl}benzimidazole.

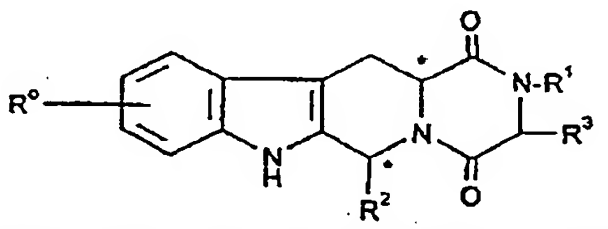
1-Benzyl-6-chloro-2-{1-[3-(1,2,4-triazol-1-yl)propyl]indol-5-ylaminocarbonyl}benzimidazole.

1-Benzyl-6-chloro-2-{1-[3-(3,5-dimethylisoxazol-4-ylcarbonylamino)propyl]indol-5-ylaminocarbonyl}benzimidazole.

1-Benzyl-6-chloro-2-{1-[3-(4-phenyl-4-hydroxypiperidin-1-yl)propyl]indol-5-ylaminocarbonyl}-benzimidazole.

1-Benzyl-6-chloro-2-{4-[3-(pyridin-2-ylcarbonylamino)propyl]-3,4-dihydro-1,4(2H)-benzoxazin-7-ylaminocarbonyl}benzimidazole.

WO 97/03675 discloses compounds of the formula

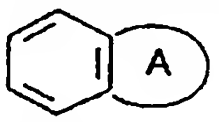


(I)

and salts and solvates (e.g. hydrates) thereof, in which:

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring  attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain;

for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

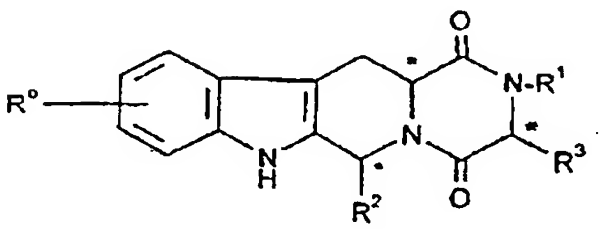
Preferred compounds include:

Cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2', 1' : 6,1]pyrido[3,4-b]indole-1,4-dione;
Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;
(6R, 12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2', 1' : 6,1] pyrido [3,4-b] indole-1,4-dione;
(5aR, 12R, 14aS)-1,2,3,5,6,11,12,14a-Octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo[1",2" : 4',5']pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-5-1,4-dione;
Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(3S, 6R,12aR)-2,3,6,7,12,12a-hexahydro-3-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;

and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

WO 97/03985 discloses compounds of the formula



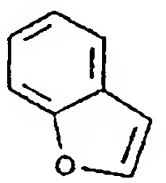
(I)

and solvates thereof, in which:

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen or C_{1-6}alkyl;

R^2 represents the bicyclic ring



which may be optionally substituted by one or more groups selected from halogen and C_{1-3}alkyl;

and

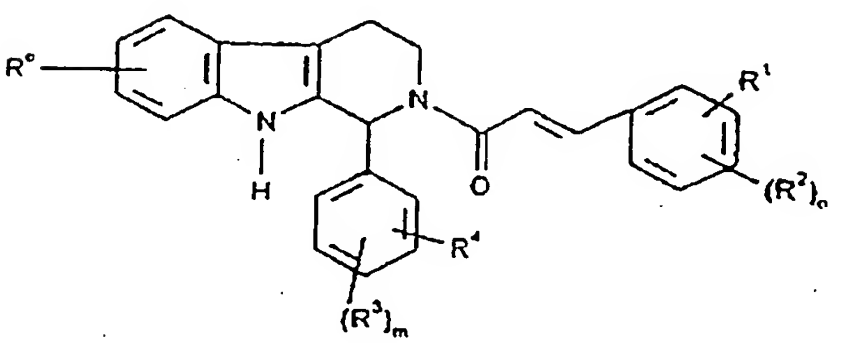
R^3 represents hydrogen or C_{1-3}alkyl.

Preferred compounds include:

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-2-methyl-pyrazino [2',1':6,1]pyrido[3,4-b]indole-1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-pyrazino[2',1':6,1] pyrido [3,4-b]indole-1,4-dione;
(3S, 6R, 12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-3-methyl-pyrazino[2',1':6,1] pyrido [3,4-b]indole-1,4-dione;

(3S, 6R, 12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-2,3-dimethyl-pyrazino[2',1':6,1] pyrido [3,4-b]indole-1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-2-isopropyl-pyrazino [2',1':6,1] pyrido [3,4-b]indole-1,4-dione;
and physiologically acceptable solvates thereof.

WO 97/43287 discloses compounds of the formula



(I)

wherein

R^0 represents -hydrogen or -halogen;

R^1 is selected from the group consisting of:

-hydrogen,

$-NO_2$,

-trifluoromethyl,

-trifluoromethoxy,

-halogen,

-cyano,

a 5- or 6- membered heterocyclic group containing at least one heteroatom selected from oxygen, nitrogen and sulphur (optionally substituted by - $C(=O)OR^a$ or C_{1-4}alkyl),

-C_{1-6}alkyl optionally substituted by -OR^a,

-C_{1-3}alkoxy,

-$C(=O)R^a$,

-O-$C(=O)R^a$,

-$C(=O)OR^a$,

-C_{1-4}alkylene $C(=O)OR^a$,

-O-C_{1-4}alkylene -$C(=O)OR^a$,

-C_{1-4}alkylene-O-C_{1-4}alkylene-$C(=O)OR^a$,

-$C(=O)NR^aSO_2R^c$,

-$C(=O)C_{1-4}$alkylene Het, wherein Het represents 5- or 6-membered heterocyclic group as defined above,

-C_{1-4}alkylene NR^aR^b,

-C_{2-6}alkenyleneNR^aR^b,

-$C(=O)NR^aR^b$,

-$C(=O)NR^aR^c$,

-$C(=O)NR^aC_{1-4}$alkylene OR^b

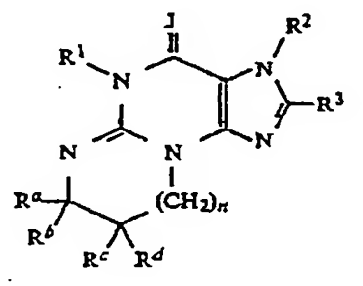
-$C(=O)NR^aC_{1-4}$alkylene Het, wherein Het represents a 5- or 6-membered

heterocyclic group as defined above,
-OR^a
-OC_{2-4}alkylene NR^aR^b,
-OC_{1-4}alkylene-$CH(OR^a)CH_2$ NR^aR^b,
-O-C_{1-4}alkylene Het, wherein Het represents a 5- or 6- membered heterocyclic group as defined above,
-O-C_{2-4}alkylene-OR^a,
-O-C_{2-4}alkylene-NR^a-C(=O)-OR^b,
-NR^aR^b,
-NR^aC_{1-4}alkyleneNR^aR^b,
-$NR^aC(=O)R^b$,
-$NR^aC(=O)NR^aR^b$,
-$N(SO_2C_{1-4}alkyl)_2$,
-$NR^a(SO_2C_{1-4}alkyl)$,
-$SO_2NR^aR^b$, and
-OSO_2trifluoromethyl;
R^2 is selected from the group consisting of:
-hydrogen,
-halogen,
-OR^a,
-C_{1-6} alkyl,
-NO_2, and
-NR^aR^b,

or R^1 and R^2, together form a 3- or 4- membered alkylene or alkenylene chain, optionally containing at least one heteratom ;
R^3 is selected from the group consisting of:
-hydrogen,
-halogen,
-NO_2,
-trifluoromethoxy,
-C_{1-6}alkyl, and
-$C(=O)OR^a$;
R^4 is hydrogen,
or R^3 and R^4 together form a 3- or 4- membered alkylene or alkenylene chain, optionally containing at least one heteratom;
R^a and R^b, which may be the same or different, are independently selected from hydrogen and C_{1-6}alkyl;
R^c represents phenyl or C_{4-6}cycloalkyl, which phenyl or C_{4-6}cycloalkyl can be optionally substituted by one or more halogen atoms, one or more -$C(=O)OR^a$ or one or more -OR^a;

n is an integer selected from 1, 2 and 3;
m is an integer selected from 1 and 2;
and pharmaceutically acceptable salts and solvates thereof.

U.S. Patent No. 5,393,755 discloses compounds of the formula



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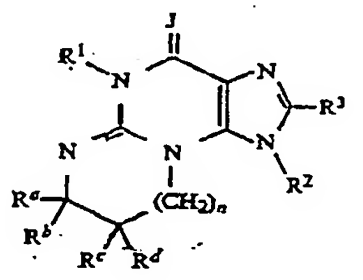
or



(I')

wherein

J is oxygen or sulfur,

R^1 is hydrogen, alkyl or alkyl substituted with aryl or hydroxy;

R^2 is hydrogen, aryl, heteroaryl, cycloalkyl, alkyl or alkyl substituted with aryl, heteroaryl, hydroxy, alkoxy, amino, monoalkyl amino or dialkylamino, or $-(CH_2)_mTCOR^{20}$ wherein m is an integer from 1 to 6, T is oxygen or —NH— and R^{20} is hydrogen, aryl, heteroaryl, alkyl or alkyl substituted with aryl or heteroaryl;

R^3 is hydrogen, halo, trifluoromethyl, alkoxy, alkylthio, alkyl, cycloalkyl, aryl, aminosulfonyl, amino, monoalkylamino, dialkylamino, hydroxyalkylamino, aminoalkylamino, carboxy, alkoxycarbonyl or aminocarbonyl or alkyl substituted with aryl, hydroxy, alkoxy, amino, monoalkylamino or dialkylamino;

R^a, R^b, R^c and R^d independently represent hydrogen, alkyl, cycloalkyl or aryl; or (R^a and R^b) or (R^c and R^d) or (R^b and R^c) can complete a saturated ring of 5- to 7-carbon atoms, or (R^a and R^b) taken together and (R^b and R^c) taken together, each complete a saturated ring of 5- to 7-carbon atoms, wherein each ring optionally can contain a sulfur or oxygen atom and whose carbon atoms may be optionally substituted with one or more or the following: alkenyl, alkynyl, hydroxy, carboxy, alkoxycarbonyl, alkyl or alkyl substituted with hydroxy, carboxy or alkoxycarbonyl; or such saturated ring can have two adjacent carbon atoms which are shared with an adjoining aryl ring; and

n is zero or one.

Preferred compounds include:

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(phenylmethyl)cyclopenta[4,5]imidazo[2,1-b]purin-4-one;
7,8-Dihydro-5-methyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
5,7,8,9-Tetrahydro-5-methyl-3-(phenylmethyl)-pyrimido[2,1-b]purin-4(3H)-one;
7,8-Dihydro-8-phenyl-5-methyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
5', 7'-Dihydro-5'-methyl-3'-(phenylmethyl)spiro[cyclohexane-1,8'-(8H)imidazo[2,1-b]purin]-4'(3'H)-one;
cis-5,6a,11,11a-Tetrahydro-5-methyl-3-(phenylmethyl-)indeno[1',2':4,5]imidazo[2,1-b]purin-4(3H)-one;
5',7'-Dihydro-2',5'dimethyl-3'-(phenylmethyl)spiro{cyclohexane-1,7'(8'H)-imidazo[2,1-b]purin}-4'-(3'H)-one;
7,8-Dihydro-2,5,7,7,8(R,S)-pentamethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
cis-5,6a,7,11b-Tetrahydro-5-methyl-3-(phenylmethyl-)indeno[2',1',:4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4-(3H)-one;
5'-Methyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'-(8'H)-(3'H)imidazo[2,1-b]purin]-4-(5'H)-one;
7,8-Dihydro-2,5,7,7-tetramethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5'H)-one;
7,8-Dihydro-7(R)-phenyl-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-3,7(R)-bis(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
(±)-7,8-Dihydro-2,5-dimethyl-7-ethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
6a(S)-7,8,9,10,10a(R)-Hexhydro-2,5-dimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
6a(R)-7,8,9,10,10a(S)-hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R)-isopropyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5,7(R)-trimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
cis-7,7a,8,9,10,10a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H-cyclopenta[5,6]pyrimido[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylpropyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R)-(2-methylpropyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R,S)-(methoxycarbonyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R,S)-(1-propyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylethyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5,7,7,8(R,S)-pentamethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
5,7,8,9-Tetrahydro-2,5,7,9(R,S)-pentamethyl-3-(phenylmethyl)-pyrimido[2,1-b]purin-4(3H)-one;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(S),7,8,9,9a(R)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-6a,7,8,9,10,10a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H -benzimidazo[2,1-b]purin-4(5H)-one;

5',7'-Dihydro-2',5'-dimethyl-3'-(phenylmethyl)spiro[cyclohexane-1,8-(8H)-imidazo[2,1-b]purin]-4-(3'H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclohept[6,7]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4-(5H)-one;

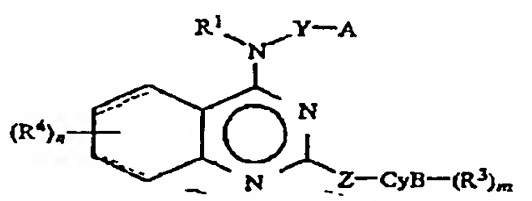
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-phenyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-2-phenyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
cis-5,6a,7,8.9,9a-Hexahydro-5-methylcyclopenta[4,-5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethylcyclopenta[4,-5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a(R), 7,8,9,9a(S)-Hexahydro-2,5-di-methylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
2',5'-dimethyl-spiro{cyclopentane-1,7'-(8'H)-(3'H)-imidazo[2,1-b]purin}-4'(5'H)-one;
7,8-Dihydro-2,5-dimethyl-7(R)-(1-methylethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5,7,7-tetramethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-di methyl-7(S)-(1-methylethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
6a(R),7,8,9,10,10a(S)-Hexahydro-2,5-dimethyl-3H-benzimidazo[2,1-b]purin-4(5H)-one;
5',7'-Dihydro-2',5'-dimethylspiro{cyclohexane-1,7-(8'H)-imidazo[2,1-b]purin}-4'(3'H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(phenylmethyl)cyclopenta[4,5]imidazo[2,1-b]purin-4(3H)-thione;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-thione;
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(4-chlorophenylmethyl)cyclopenta[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(cyclohexylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(2-naphthylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(4-bromophenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R)-7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(4-methoxyphenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2,3,5-trimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2-(hydroxymethyl)-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2-methylthio-5-methyl-3-(Phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-3,4,5,6a,7,8,9,9a-Octahydro-5-methyl-4-oxo-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-2-carboxylic acid;
cis-3,4,5,6a,7,8,9,9a-Octahydro-5-methyl-4-oxo-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-2-

carboxylic acid, methyl ester;
cis-5,6a,7,8,9,9a-Hexahydro-2-bromo-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one;
cis-5,6a,7,8,9,9a-Hexahydro-2-(methylaminosulfonyl)-5-methyl-3-(phenylmethyl)cyclopent[4,-5]imidazo[2,1-b]purin-4(3H)one;
cis-1-Cyclopentyl-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo[2,1-b]purin-4-(1H)one;
cis-5,6a,7,8,9,9a-Hexahydro-3,5-bis-(phenylmethyl)cyclopent(4,5)imidazo(2,1-b)purin-4(3H)one;
cis-6a,7,8,9,10,10a-Hexahydro-3,5-bis-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)one;
cis-3-Cyclopentyl-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo(2,1-b)purin-4(3H)one;
5'-Methyl-3'-(phenylmethyl)spiro[cyclopentane-1,7-(8'H)-(3'H)imidazo[2,1-b]purin]-4-(5H)one;
2',5'-Dimethyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7-(8'H)-(3H)imidazo[2,1-b]purin]-4-(5'H)one;
cis-5,6a,(R)7,8,9,9a(S)-Hexahydro-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo(2,1-b)purin-4(3H)one;
cis-3-Cyclopentyl-5,6a,7,8,9,9a-Hexahydro-2,5-dimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)one;
5'-Methyl-2'-trifluoromethyl-3'-(phenylmethyl)spiro{cyclo-pentane-1,7'(8'H)-(3'H)imidazo[2,1-b]purin}-4-(5'H)-one;
7,8-Dihydro-5,7,7-trimethyl-2-trifluoromethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
(+/−)-cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-trifluoromethyl-3-(phenylmethyl)cyclopent[4,-5]imidazo[2,1-b]purin-4(3H)-one;
(+/−)-6a,7,8,9,9a,10,11,11 a-Octahydro-2,5-dimethyl-3-(phenylmethyl)-3H-pentaleno[6a',1':4,-5]imidazo[2,1-b]purin-4(5H)-one;
(+)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-phenylmethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one;
(−)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-phenylmethyl-3H-pentaleno[6a',1':4,5]Imidazo[2,1-b]purin-4(5H)-one;
(+/−) 6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one;
(+)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one;
(−)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one;
6a,7,8,9,10,10a,11,12,13,13a-Decahydro-2,5-dimethyl-(3-phenylmethyl)napth[1,8a-d]imidazo[2,1-b]purin-4(5H)one;
7(R)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(3H)-one;
7(R)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
7(S)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(3H)-one;
7(S)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(trimethylacetoxy)methyl]-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(4-pyridylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;

5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[2-(1-morpholinyl)ethyl]cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[acetoxymethyl]cyclopent[4,5]imidazo[2.1-b]purin-4(3H)-one;
5,6a,7,8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R),7(S),8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;

5,6a(S),7(R),8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-6a,7,8,9, 10,10a-Hexahydro-2,5,7-trimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2,5,6a-trimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3H); or
cis-6a,7,8,9,10,10a-Hexahydro-2,5,7-trimethyl-3H-benzimidazo[2,1-b]purin-4(5H)-one].

U.S. Patent No. 5,439,895 discloses compounds of the formula



(I)

wherein R^1 is hydrogen or C1–4 alkyl;
Y is C1–6 alkylene;
A is —O—R^0 or —S(O)p—R^0,
in which R^0 is C1–4 alkyl-hydroxy;
p is 0–2;
Z is single bond, methylene, ethylene, vinylene or ethynylene;
CyB is
(1) 7-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one, two or three nitrogen atoms,
(2) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, two or three nitrogen atoms,
(3) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atom, one nitrogen atom,
(4) 4- or 5-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one, two or three nitrogen atoms, or
(5) 4–7 membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one or two oxygen atoms, or one or two sulfur atoms;
R^3 is hydrogen, C1–4 alkyl, C1–4 alkoxy, halogen or trifluoromethyl;
R^4 is (1) hydrogen, (2) C1–4 alkyl, (3) C1–4 alkoxy, (4) —$COOR^8$, in which R^8 is hydrogen or C1–4 alkyl, (5) —NR^9R^{10}, in which R^9 is hydrogen, C1–4 alkyl or phenyl(C1–4 alkyl) and R^{10} is hydrogen or C1–4 alkyl, (6) —$NHCOR^{11}$, in which R^{11} is C1–4 alkyl, (7) —$NHSO_2R^{11}$, in which R^{11} is as hereinbefore defined, (8) $SO_2NR^9R^{10}$, in which R^9 and R^{10} are as hereinbefore defined, (9) —$OCOR^{11}$, in which R^{11} is as hereinbefore defined, (10) halogen, (11) trifluoromethyl, (12) hydroxy, (13) nitro,

(14) cyano, (15) $-SO_2N=CHNR^{12}R^{13}$ in which R^{12} is hydrogen or C1–4 alkyl and R^{13} is C1–4 alkyl, (16) $-CONR^{14}R^{15}$ in which R^{14} is hydrogen or C1–4 alkyl and R^{15} is C1–4 alkyl or phenyl(C1–4 alkyl), (17) C1–4 alkylthio, (18) C1–4 alkylsulfinyl, (19) C1–4 alkylsulfonyl, (20) ethynyl, (21) hydroxymethyl, (22) tri(C1–4 alkyl)silylethynyl or (23) acetyl; and m and n independently are 1 or 2; with the proviso that

(1) a CyB ring does not bond to Z through a nitrogen atom in the CyB ring when Z is vinylene or ethynylene;

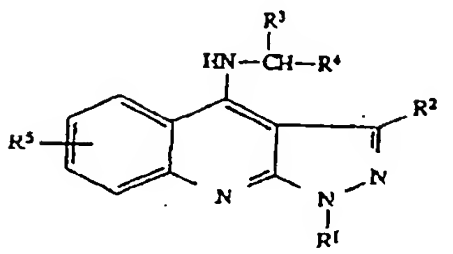
or pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof.

Preferred compounds include:

4-[2-(2-hydroxycthoxy)ethyl]amino-6-acetyl-2-(1-imidazolyl)quinazoline,
2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-ethynylquinazoline,
2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-(2-triisopropylsilylethynyl)quinazoline,
4-[2-(2-hydroxyethoxy)ethyl]amino-6-hydroxymethyl-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylsulfinyl-2-(1-imidazolyl)quinazoline,
6-chloro-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
4-[2-(2-hydroxyethoxy)ethyl]amino-6-methoxycarbonyl-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-6-iodo-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline or
6-methoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,

and pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof.

U.S. Patent No. 5,488,055 discloses compounds of the formula



wherein:

R^1 is lower-alkyl, phenyl-lower-alkyl, or cycloalkyl;

R^2 is hydrogen, or lower-alkyl;

R^3 is hydrogen, lower-alkyl, or hydroxylower-alkyl;

R^4 is cycloalkyl or cylcoalkyl substituted by from one to two, the same or different, substituents selected from the group consisting of lower-alkoxycarbonyl, carboxy, lower-alkylthio-lower-alkoxycarbonyl, hydroxylower-alkyl, hydroxy, oxo, lower-alkoxy, lower-alkyl, and halogen; and

R^5 is from one to three, the same or different, substituents selected from the group consisting of hydrogen, lower-alkoxy, hydroxy, dilower-alkylamino-lower-alkoxy, carboxylower-alkoxy, lower-alkoxycarbonyl-lower-alkoxy, nitro, polyhydroxylower-alkoxy, amino, epoxy-lower-alkoxy, carboxy, lower-alkanoylamino, lower-alkoxycarbonyl, pyridinyl, 4-morpholinyl-lower-alkoxy, lower-alkylsulfonyl, cyano, 1-imidazolyl, halogen, dilower-alkylaminosulfonyl, oxadiazolyl (or oxadiazolyl substituted on any available carbon atom thereof by lower-alkyl), lower-alkylsulfinyl, 1-pyrazolyl (or 1-pyrazolyl substituted on any available carbon atom thereof by lower-alkyl), trifluoromethylsulfonyl, lower-alkenyl, lower-alkyl, and lower-alkynyl; or a pharmaceutically acceptable acid-addition salt and/or hydrate and/or solvate thereof, or, where applicable, a stereoisomer or a racemic mixture thereof.

Preferred compounds include

1-ethyl-6-nitro-N-[S(+)-1-(cyclohexyl) ethyl]-1H-pyrazolo [3,4-b]quinolin-4-amine,

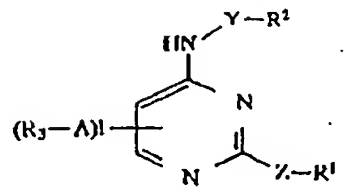
1-ethyl -6-nitro-N-[cyclohexylmethyl]- 1H-pyrazolo [3,4-b]quinolin-4-amine,

1-ethyl-6-cyano-N-[S(+)-1-(cyclohexyl)ethyl]-1H-pyrazolo [3,4-b]quinolin-4-amine,

1-ethyl-6-bromo-N-[S(+)-1-(cyclohexyl)ethyl]-1H-pyrazolo [3,4-b]quinolin-4-amine, and

1-ethyl-6-(1-pyrazolyl)-N-[S(+)-1-(cyclohexyl)ethyl]-1H-pyrazolo [3,4-b]quinolin-4-amine.

U.S. Patent No. 5,525,064 discloses compounds of the formula



(I)

wherein A is a bond, C_{1-4} alkylene or C_{1-4} oxyalkylene;

Y is a bond, C_{1-4} alkylene, C_{1-4} alkyleneoxy, C_{1-4} alkoxyphenylene or phenyl(C_{1-4})alkylene;

% is a bond or vinylene;

R^1 is a heterocyclic ring selected from the group consisting of pyrrole, pyridine, azepine, imidazole, pyrazole, pyrimidine, pyrazine, pyridazine, benzimidazole, quinoline, isoquinoline and partially or fully saturated rings thereof;

R^2 is

(i) a heterocyclic ring selected from the group consisting of pyrrole, pyridine, azepine, imidazole, pyrazole, pyrimidine, pyrazine, pyridazine, benzimidazole, quinoline, isoquinoline, furan, pyran, dioxole, dioxine, benzofuran, benzopyran, benzodioxole, benzodioxine, thiophene, thioine, benzothiophene, benzothione and partially or fully saturated rings thereof,

(ii) C_{4-15} carbocyclic ring,

(iii) C_{1-4} alkoxy,

(iv) hydroxy(C_{1-4} alkoxy), or

(v) hydroxy;

with the proviso that:

when R^1 is pyridine or pyridine substituted by one or two of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, trifluoromethyl or nitro then R^2 is a member selected only from the group consisting of benzodioxole or benzodioxole substituted by one or two of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, trifluoromethyl, nitro or a group of the formula:

—$COOR^{10}$

wherein R^{10} is hydrogen or C_{1-4} alkyl, and hydroxy(C_{1-4} alkoxy);

R^3 is

(i) a heterocyclic ring selected from the group consisting of pyrrole, pyridine, azepine, imidazole, pyrazole, pyrimidine, pyrazine, pyridazine, benzimidazole, quinoline, isoquinoline, furan, pyran, benzofuran, benzopyran, thiophene, thioine, benzothiophene, benzothione, thiazole, isothiazole, thiazine, benzothiazole, benzoisothiazole, benzothiazine and partially or fully saturated rings thereof,

(ii) C_{4-15} carbocyclic ring,

(iii) a group of formula:

CH_2=CH(X)—

wherein X is halogen, or

(iv) hydrogen,

l is 1 or 2,

with the proviso that:

the ring represented by R^1 may be substituted by one or two of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, trifluoromethyl or nitro;

the ring represented by R^2 may be substituted by one or two of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, trifluoromethyl, nitro or a group of the formula:

—COOR[10]

wherein R^{10} is hydrogen or C_{1-4} alkyl, and the ring represented by R^3 may be substituted by one or two of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, trifluoromethyl, nitro, cyano, ethynyl or a group of the formula:

—SONR[7]R[8]

wherein R^7 and R^8 are independently hydrogen or C_{1-4} alkyl, and with the proviso that:

R^2 is not hydroxy when Y is a bond; and

R^1 is not bonded through its nitrogen atom when Z is vinylene,

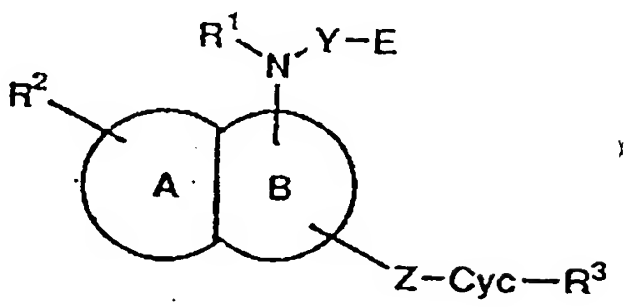
or pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable salts thereof.

Preferred compounds include

2-(1-Imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-5-(3-methoxyphenyl)methylpyrimidine,
2-(1-Imidazolyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-4-(2-methoxyethyl)aminopyrimidine,
2-(1-Imidazolyl)-5-ethyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-phenylmethyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-methyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5,6-dimethyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(3-methoxyphenyl)methyl-4-(2-methoxyethyl)aminopyrimidine,
2-(1-Imidazolyl)-5-(4-methoxyphenyl)methyl-4-[2-(2-hydroxyethoxy)ethyl]aminopyrimidine,
2-(1-Imidazolyl)-5-(4-methoxyphenyl)methyl-4-(2-methoxyethyl)aminopyrimidine or
2-(1-Imidazolyl)-5-(4-methoxyphenyl)methyl-4-phenylmethylaminopyrimidine.
2-(1-Imidazolyl)-5-phenoxymethyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(1-Imidazolyl)methyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(1-chlorovinyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thiazolyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-[2-(2-hydroxyethoxy-)ethyl]aminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(1-naphthyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(4-methoxyphenyl)methylaminopyrimidine,

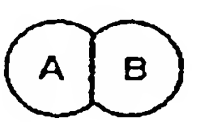
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-methoxyphenyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-furyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-thienyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-pyridyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-methoxyethyl)aminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-phenylmethoxyaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(4-chlorophenyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-chlorophenyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(4-methylphenyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(4-methoxyphenyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(5-methyl-2-thienyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-[4-(1-imidazolyl)phenyl] methylaminopyrimidine,
2-(1-Imidazolyl)-5-(3-pyridyl)-4-(1,3-dioxaindan- 5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(3-furyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(3-pyridyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(4-chlorophenyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(Benzimidazol-1-yl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(4-ethoxycarbonylphenyl-)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-naphthyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(3-Pyridyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-[2-(3-Pyridyl)vinyl]-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(2-Methyl-1-Imidazolyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine or
2-(1-Imidazolyl)-5-(2-thienyl)-4-(benzimidazol-5-yl)methylaminopyrimidine.

European published paten t application No. 0728759 discloses compounds of the formula

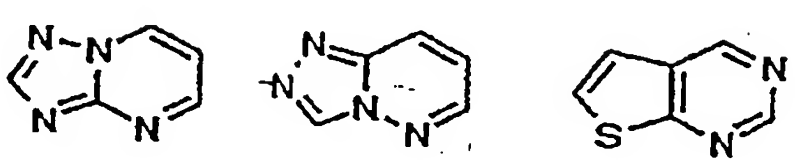


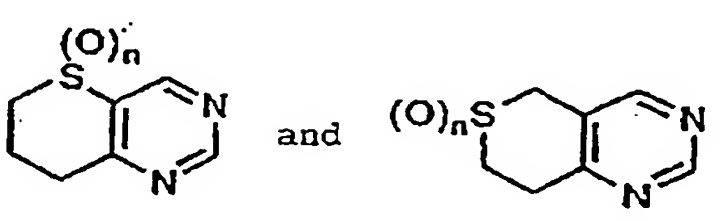
(I)

wherein



is a heterocycle selected from





;

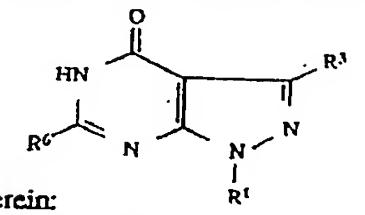
n is 0, 1 or 2;
Y is single bond or C1-6 alkylene;
Z is single bond, C1-2 alkylene or vinylene;
E is

(i) 4-15 membered, unsaturated, partially saturated or fully saturated, mono or bicyclic hetero ring containing one or two hetero atoms, chosen from nitrogen, oxygen and sulfur, not more than one hetero atom being sulfur,
(ii) 4-15 membered, unsaturated or partially saturated, mono or bicyclic carbocyclic ring, or
(iii) $-OR^4$; in which R^4 is hydrogen atom, C1-4 alkyl or C1-4 alkyl substituted by a hydroxy group;

Cyc is 5-7 membered, unsaturated, partially saturated or fully saturated, monocyclic hetero ring containing one or two nitrogen atoms or 5-7 membered, unsaturated or partially saturated, monocyclic carbocyclic ring;
R^1 is hydrogen atom or C1-4 alkyl;
R^2 is hydrogen atom, C1-4 alkyl, C1-4 alkoxy or halogen atom;
R^3 is hydrogen atom, C1-4 alkyl, C1-4 alkoxy or $-COOR^5$; in which R^5 is hydrogen atom or C1-4 alkyl;
with the proviso that

(1) a Cyc ring does not bond to Z through a nitrogen atom in the Cyc ring where Z is vinylene and that
(2) Y is not a single bond, when E is $-OR^4$; or a pharmaceutically acceptable acid addition salt, pharmaceutically acceptable salt or hydrate thereof.

U.S. Patent No. 5,541,187 discloses compounds of the formula



wherein:

R^1 is hydrogen, alkyl, cycloalkyl, cycloalkyl substituted by alkyl or hydroxyl, 2- or 3-tetrahydrofuranyl, 3-tetrahydrothienyl 1,1,-dioxide, cycloalkyl-alkyl, carboxy-alkyl, carbo-lower-alkoxy-alkyl, dialkylaminoalkyl, phenyl-lower-alkyl, phenyl-lower-alkyl in which the phenyl ring is substituted in the 2, 3, or 4-position by one or two substituents, the same or different, selected from the group consisting of amino, halogen, alkyl, carboxyl, carbo-lower-alkoxy, carbamoyl, $NHSO_2$-(quinolinyl), nitro and cyano;

R^3 is hydrogen, lower-alkyl, phenyl-lower-alkyl, lower-alkoxyphenyl-lower-alkyl, dilower-alkoxy-phenyl-lower-alkyl, pyridyl-lower-alkyl, cycloalkyl-lower-alkyl, phenylamino, dialkylamino, halogen, trifluoromethyl, lower-alkylthio, cyano or nitro; and

R^6 is a five or six membered heterocyclic ring containing from one to two nitrogen atoms, substituted—or unsubstituted—at any available carbon atom by one or two substituents, the same or different, selected from the group consisting of lower-alkyl, halogen, lower-alkoxy, cycloalkyloxy, 4-morpholinyl,. lower-alkoxy-lower-alkoxy, hydroxy, imidazolyl, oxo and 4-morpholinyl-lower-alkoxy; or at any available nitrogen atom by lower-alkyl, lower-alkanoyl, or trifluoroacetyl; or a pharmaceutically acceptable acid-addition salt thereof.

Preferred compounds include:

1-Cyclopentyl-3-methyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimidin-4-one,

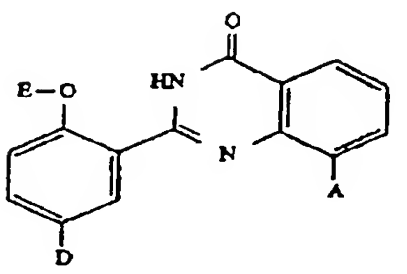
1-Cyclopentyl-3-ethyl-6-(3-ethoxy-4-pyridyl)pyrazolo[3,4-d]pyrimidin-4-one,

1-Cyclopentyl-3-ethyl-6-(3-methoxy-4-pyridyl)pyrazolo[3,4-d]pyrimidin-4-one,

1-Cyclopentyl-3-trifluoromethyl-6-(3-ethoxy-4-pyridyl)pyrazolo[3,4-d]pyrimidin-4-one,

1-Cyclopentyl-3-ethyl-6-(2-(1-imidazolyl)-4-pyridyl)pyrazolo[3,4-d]pyrimidin-4-one,

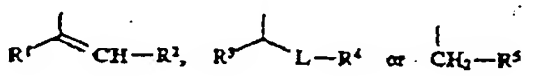
U.S. Patent No. 5,721,238 discloses compounds of the formula



(I)

in which

A represents oxiranyl, which is optionally substituted by straight-chain or branched alkyl having up to 8 carbon atoms, which in turn can be substituted by phenyl, or represents a radical of the formula



wherein

R^1 denotes hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,

R^2 denotes straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by phenyl,

R^3 denotes straight-chain or branched alkyl having up to 5 carbon atoms or a group of the formula $-OR^6$,

wherein

R^6 denotes hydrogen, a hydroxyl-protecting group or straight-chain or branched alkyl having up to 5 carbon atoms,

R^4 denotes straight-chain or branched alkyl having 2 to 10 carbon atoms, which is optionally substituted by phenyl,

L denotes a radical of the formula —CO—, —CH(OH), $-CH_2$, $-CH(N_3)$ or $-CH(OSO_2R^7)$,

wherein

R^7 denotes straight-chain or branched alkyl having up to 4 carbon atoms or phenyl,

R^5 denotes straight-chain or branched alkyl having 3 to 8 carbon atoms which is substituted by phenyl, or denotes benzyl or 2-phenylethyl,

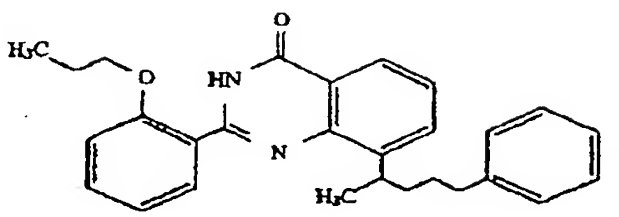
D represents hydrogen, or represents a group of the formula $-SO_2-NR^8R^9$,

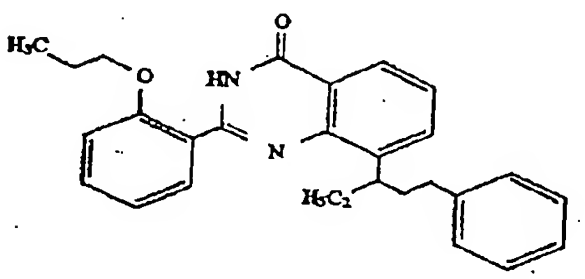
wherein

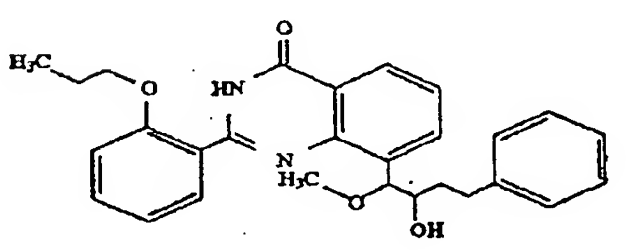
R^8 and R^9 are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, or, together with the nitrogen atom, form a 5- to 6-membered saturated heterocyclic radical which has up to 2 further hetero atoms from the series consisting of S, N and/or O and is optionally substituted, including via a free N function, by straight-chain or branched alkyl having up to 6 carbon atoms, which in turn can be substituted by hydroxyl, and

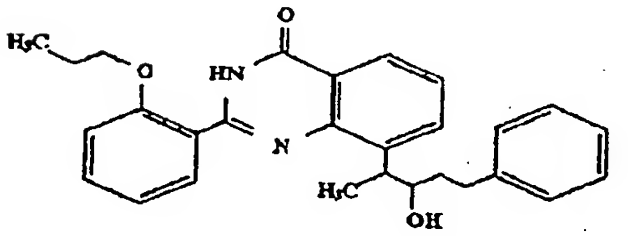
E represents straight-chain or branched alkyl having up to 8 carbon atoms, and tautomers and salts thereof.

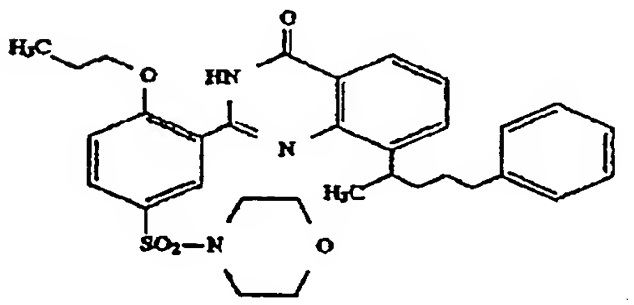
Preferred compounds include:

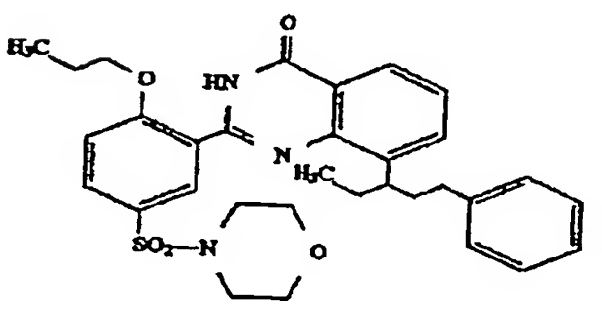




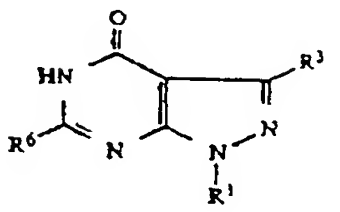








U.S. Patent No. 5,294,612 discloses compounds of the formula



wherein:

R^1 is hydrogen, alkyl, C_4 to C_7 cycloalkyl, C_4 to C_7 cycloalkyl substituted by C_1 to C_{10} alkyl or hydroxyl, 2- or 3-tetrahydrofuranyl, 3-tetrahydrothienyl 1,1, -dioxide, C_4 to C_7 cycloalkyl-C_1 to C_{10} alkyl, carboxy-C_1 to C_{10} alkyl, carbo-C_1 to C_4 lower-alkoxy-C_1 to C_{10} alkyl, dialkylamino C_1 to C_{10} alkyl, phenyl-C_1 to C_4 lower-alkyl, phenyl-C_1 to C_4 lower-alkyl in which the phenyl ring is substituted in the 2, 3, or 4-position by one or two substituents, the same or different, selected from the group consisting of amino, halogen, C_1 to C_{10} alkyl, carboxyl, carbo-C_1 to C_4 lower-alkoxy, carbamoyl, $NHSO_2$-(quinolinyl), nitro and cyano;

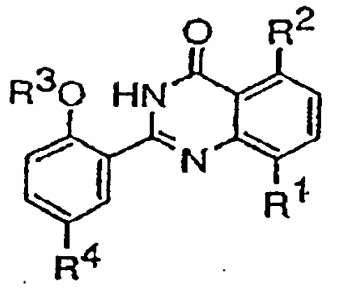
R^3 is, C_1 to C_4 lower-alkyl, phenyl-C_1 to C_4 lower-alkyl, lower-alkoxyphenyl-C_1 to C_4 lower-alkyl, diC_1 to C_4 lower-alkoxy-phenyl-C_1 to C_4 lower-alkyl, pyridyl-C_1 to C_4 lower-alkyl, C_4 to C_7 cycloalkyl-C_1 to C_4 lower-alkyl, phenylamino, diC_1 to C_{10} alkylamino, halogen, trifluoromethyl, C_1 to C_4 lower-alkylthio, cyano or nitro; and

R^6 is a nine or ten membered bicyclic ring having carbon and from one to two nitrogen atoms, and the heterocycle is made up of fused 5 or 6 membered rings or such ring substituted at any available carbon atom by one or two substituents, the same or different, selected from the group consisting of C_1 to C_4 lower-alkyl, halogen, C_1 to C_4 lower-alkoxy, C_4 to C_7 cycloalkyloxy, 4-morpholinyl, C_1 to C_4 lower-alkoxy-C_1 to C_4 lower-alkoxy, hydroxy, imidazolyl, oxo and 4-morpholinyl-C_1 to C_4 lower-alkoxy, or at any available nitrogen atom by C_1 to C_4 lower-alkyl, C_2 to C_4 lower-alkanoyl, or trifluoroacetyl; or a pharmaceutically acceptable acid-addition salt thereof.

Preferred compounds include:

1-Cyclopentyl-3-methyl-6-(4-quinolinyl)-pyrazolo[3,4-d]pyrimidin-4-one

WO 93/12095 discloses compounds of the formula



(I)

or a pharmaceutically acceptable salt thereof,

wherein R^1 is H, C_1-C_4 alkyl, C_1-C_4 alkoxy or $CONR^5R^6$;

R^2 is H or C_1-C_4 alkyl;

R^3 is C_2-C_4 alkyl;

R^4 is H, C_2-C_4 alkanoyl optionally substituted with NR^7R^8, (hydroxy)C_2-C_4 alkyl optionally substituted with NR^7R^8, $CH=CHCO_2R^9$, $CH=CHCONR^7R^8$, $CH_2CH_2CO_2R^9$, $CH_2CH_2CONR^7R^8$, $SO_2NR^7R^8$, $SO_2NH(CH_2)_nNR^7R^8$ or imidazolyl;

R^5 and R^6 are each independently H or C_1-C_4 alkyl;

R^7 and R^8 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino or 4-(NR^{10})-1-piperazinyl group wherein any of said groups is optionally substituted with $CONR^5R^6$;

R^9 is H or C_1-C_4 alkyl;

R^{10} is H, C_1-C_3 alkyl or (hydroxy)C_2-C_3 alkyl;

and n is 2, 3 or 4;

with the proviso that R^4 is not H when R^1 is H, C_1-C_4 alkyl or C_1-C_4 alkoxy.

Preferred compounds include:

2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-8-methylquinazolin-4-(3H)-one;

2-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-8-methylquinazolin-4(3H)-one;

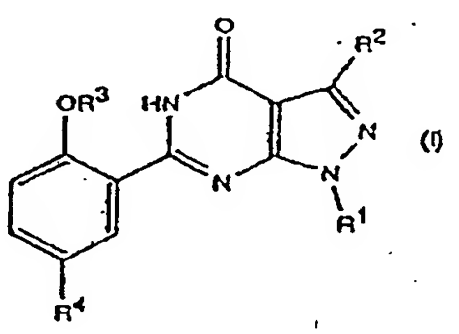
8-methyl-2-{5-[2-(4-methyl-1-piperazinylcarbonyl)-ethenyl]-2-n-propoxyphenyl}quinazolin-4(3H)-one;

8-carbamoyl-2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]phenyl}quinazolin-4(3H)-one;

and 8-ethylcarbamoyl-2-(2-n-propoxyphenyl)quinazolin-4(3H)-one;

and pharmaceutically acceptable salts thereof.

WO 93/07149 discloses compounds of the formula



(I)

or a pharmaceutically acceptable salt thereof,

wherein R^1 is C_1-C_6 alkyl;

R^2 is H, methyl or ethyl;

R^3 is C_2-C_4 alkyl;

R^4 is C_1-C_4 alkyl optionally substituted with NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; $SO_2NR^5R^6$; $CONR^5R^6$; CO_2R^7; or halo;

R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl group wherein said group is optionally substituted by one or two C_1-C_4 alkyl groups;

R^7 is H or C_1-C_4 alkyl;

and R^8 is H, C_1-C_3 alkyl or hydroxy C_2-C_3 alkyl.

Preferred compounds include:

6-(5-bromo-2-n-propoxyphenyl)-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-(5-morpholinosulphonyl-2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[5-(2-carboxyvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

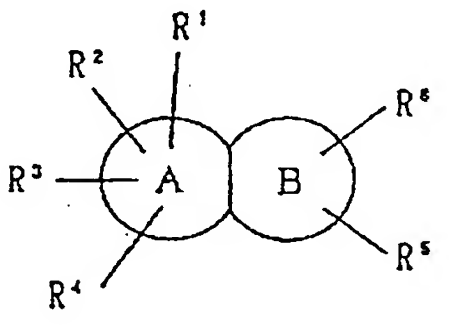
6-[5-(2-t-butoxycarbonylvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-[5-(2-morpholinocarbonylvinyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

and 3-methyl-6-[5-(2-morpholinocarbonylethyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

and pharmaceutically acceptable salts thereof.

European published patent application No. 0607439 discloses compounds of the formula

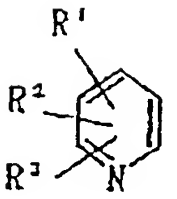


(1)

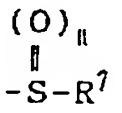
[in formula (1), ring A represents a benzene ring, a pyridine ring or a cyclohexane ring; ring B represents a pyridine ring, a pyrimidine ring, or an imidazole ring.

Provided that the ring A and the ring B are combined sharing two atoms and the atoms shared may be either a carbon atom or a nitrogen atom.

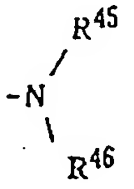
In the case where the ring A is a pyridine ring and that except the case where the ring B shares the nitrogen atom of this pyridine ring to combine therewith, the ring A is represented by



R^1, R^2, R^3 and R^4, each of which may be the same or different from one another, represent each a hydrogen atom, a halogen atom, a lower alkyl group which may be substituted with a halogen atom, a cycloalkyl group which may be substituted, a lower alkoxy group, a hydroxyalkyl group, a nitro group, a cyano group, an acylamino group, a carboxyl group which may be protected, a group represented by the formula

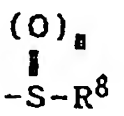


(wherein R^7 represents a lower alkyl group, and n represents 0 or an integer of 1 to 2), or a group represented by the formula

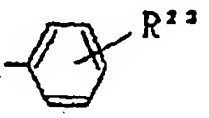


(wherein R^{45} and R^{46}, each of which may be the same or different from each other, represent each a hydrogen atom or a lower alkyl group; or R^{45} and R^{46} can form a ring which may contain another nitrogen atom or oxygen atom together with the nitrogen atom to which they are bonded with the proviso that this ring may be substituted); or, two of R^1, R^2, R^3 and R^4 may together form methylenedioxy, ethylenedioxy or a phenyl ring.

R^5 represents a hydrogen atom, a halogen atom, a hydroxyl group, a hydrazino group, a lower alkyl group, a cycloalkyl group which may be substituted, a lower alkoxy group, a lower alkenyl group, a carboxyalkyl group which may be protected, a carboxyalkenyl group which may be protected, a hydroxyalkyl group, a carboxyl group which may be protected, a group represented by the formula



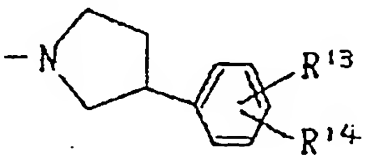
(wherein R^8 represents a lower alkyl group, and m represents 0 or an integer of 1 to 2), a group represented by the formula $-O-R^9$ (wherein R^9 represents a hydroxyalkyl group which may be protected, a carboxyalkyl group which may be protected or a benzyl group which may be substituted), a group represented by the formula



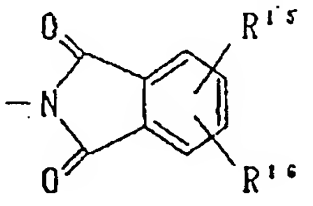
(wherein R^{23} represents a hydroxyl group, a lower alkyl group, a lower alkoxy group, a hydroxyalkyl group or a hydroxyalkyloxy group), a heteroaryl group which may be substituted, a 1,3-benzdioxolyl group which may be substituted, a 1,4-benzdioxyl group which may be substituted, a 1,3-benzdioxolylalkyl group which may be substituted, a 1,4-benzdioxylalkyl group which may be substituted, a group represented by the formula $-C(R^{24})=X$ [wherein X represents an oxygen atom, a sulfur atom or a group represented by the formula $=N-R^{10}$ (wherein R^{10} represents a hydroxyl group, a cyano group or a carboxyalkyloxy group which may be protected); and R^{24} represents a hydrogen atom or a lower alkyl group], or a group represented by the formula $-NR^{11}R^{12}$ (wherein R^{11} and R^{12}, each of which may

be the same or different from each other, represent each a hydrogen atom, a lower alkyl group, a hydroxyalkyl group, an aminoalkyl group, a carboxyalkyl group which may be protected, an alkylcarbamoyl group, a carboxyalkylcarbamoyl group which may be protected, a heteroarylalkyl group which may be substituted, a 1,3-benzoxolylalkyl group or a 1,4-benzdioxylalkyl group; or, further, R^{11} and R^{12} can form a ring which may contain another nitrogen atom or oxygen atom together with a nitrogen atom to which they are bonded with the proviso that this ring may be substituted).

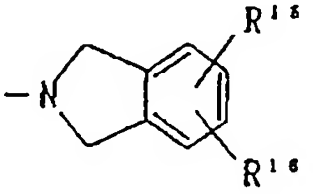
R^6 represents a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a lower alkyl group, a lower alkoxy group, a lower alkenyl group, a 1,3-benzdioxolylalkyloxy group, a 1,4-benzdioxylalkyloxy group, a phenylalkyloxy group which may be substituted, a group represented by the formula



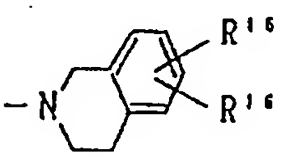
(wherein R^{13} and R^{14}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{13} and R^{14} may together form methylenedioxy or ethylenedioxy), a group represented by the formula



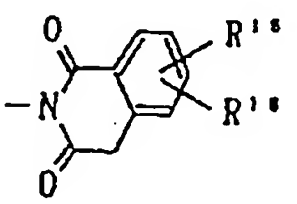
a group represented by the formula



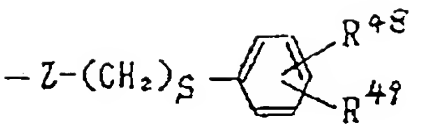
a group represented by the formula



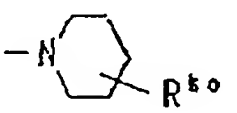
a group represented by the formula



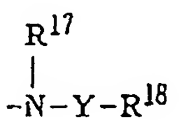
(in these formulas, R^{15} and R^{16}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{15} and R^{16} may together form methylenedioxy or ethylenedioxy), a piperidne-4-spiro-2'-dioxan-1-yl group, a group represented by the formula



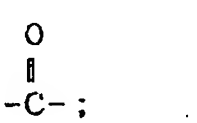
(wherein R^{48} and R^{49}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{48} and R^{49} may together form methylenedioxy or ethylenedioxy; and Z represents a sulfur atom or an oxygen atom), a group represented by the formula



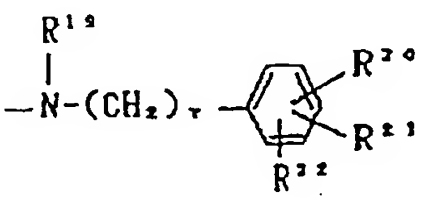
(wherein R^{50} represents a hydroxyl group, a halogen atom, a lower alkyl group, a lower alkoxy group, a carboxyl group which may be protected, a cyano group, a hydroxyalkyl group or a carboxyalkyl group), a group represented by the formula



[wherein R^{17} represents a hydrogen atom, a lower alkyl group, an acyl group, a lower alkoxyalkyl group, a carboxyalkyl group which may be protected or a hydroxyalkyl group; Y represents a group represented by the formula $-(CH_2)_q-$ (wherein q is 0 or an integer of 1 to 8), or a group represented by the formula

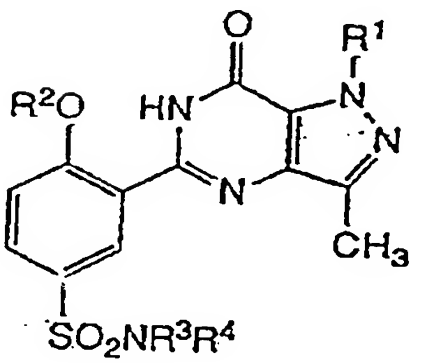


further, in the group represented by the formula $-(CH_2)_q-$, when q is an integer of 1 to 8, each carbon atom may have 1 to 2 substituent(s); and R^{18} represents a hydrogen atom, a hydroxyl group, a carboxyl group which may be protected, a cyano group, an acyl group, a heteroaryl group which may be substituted or a cycloalkyl group which may be substituted], or a group represented by the formula



(wherein R^{19} represents a hydrogen atom, a lower alkyl group, a lower alkoxyalkyl group, an acyl group, a carboxyalkyl group which may be protected or a hydroxyalkyl group; R^{20}, R^{21} and R^{22}, each of which may be the same or different from one another, represent each a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a nitro group, a lower alkyl group, a lower alkoxy group, a lower alkoxyalkyl group, a lower alkenyl group, an acyl group, an acylamino group, an alkylsulfonylamino group, a hydroxyiminoalkyl group, an alkyloxycarbonylamino group, an alkyloxycarbonyloxy group or a heteroaryl group which may be substituted; or, further, two of R^{20}, R^{21} and R^{22} may together form a saturated or unsaturated ring which may contain a nitrogen atom, a sulfur atom or an oxygen atom; and r represents 0 or an integer of 1 to 8)].

WO 93/06104 discloses compounds of the formula



(I)

or a pharmaceutically acceptable salt thereof,

wherein R^1 is methyl or ethyl;

R^2 is ethyl or n-propyl;

and R^3 and R^4 are each indepdendently H, or C_1–C_6 alkyl optionally substituted with C_5–C_7 cycloalkyl or with morpholino.

Preferred compounds include:

5-[2-ethoxy-5-(3-morpholinopropylsulphamoyl)-phenyl]-1,3-dimethyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;

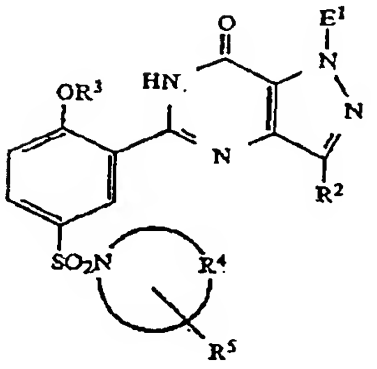
1-ethyl-5-[5-(n-hexylsulphamoyl)-2-n-propoxy-phenyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

1-ethyl-5-(5-diethylsulphamoyl-2-n-propoxy-phenyl)-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;

and 5-[5-(N-cyclohexylmethyl-N-methylsulphamoyl)-2-n-propoxyphenyl]-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

and pharmaceutically acceptable salts thereof.

U.S. Patent No. 5,346,901 discloses compounds of the formula



(I)

wherein

R^1 is H, C_1–C_3 alkyl, C_3–C_5 cycloalkyl or C_1–C_3 perfluoroalkyl;

R^2 is H, C_1–C_6 alkyl optionally substituted by OH, C_1–C_3 alkoxy or C_3–C_6 cycloalkyl, or C_1–C_3 perfluoroalkyl;

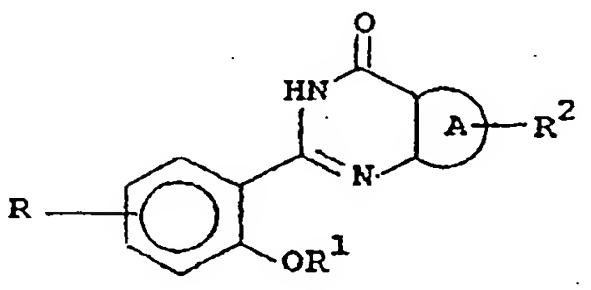
R^3 is C_1–C_6 alkyl, C_3–C_6 alkenyl, C_3–C_6 alkynyl, C_3–C_7 cycloalkyl, C_1–C_6 perfluoroalkyl or (C_3–C_6 cycloalkyl)C_1–C_6 alkyl;

R^4 taken together with the nitrogen atom to which it is attached completes a pyrrolidinyl, piperidino, or morpholino group;

R^5 is H, C_1–C_4 alkyl, C_1–C_3 alkoxy, NR^7R^8, or $CONR^7R^8$;

R^7 and R^8 are each independently H, C_1–C_4 alkyl, (C_1–C_3 alkoxy)C_2–C_4 alkyl or hydroxy C_2–C_4 alkyl; and pharmaceutically acceptable salts thereof.

European published patent application No. 0442204 discloses compounds of the formula



(1)

or a pharmaceutically acceptable salt thereof, wherein

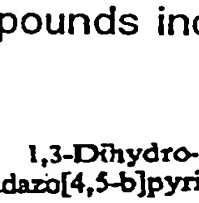
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkyl C_{1-6}alkyl, or C_{1-6}alkyl substituted by 1 to 6 fluoro groups ;

R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6}alkyl, phenyl, -$NHCOR^3$ wherein R^3 is hydrogen or C_{1-6} alkyl, or -NR^4R^5, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5}cycloalkyl or C_{1-6}alkyl which is optionally substituted by -CF_3, phenyl, -$S(O)_nC_{1-6}$ alkyl wherein

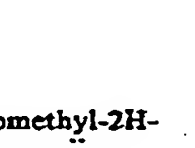
n is 0, 1 or 2, -OR^6, -CO_2R^7 or -NR^8R^9 wherein R^8 to R^9 are independently hydrogen or C_{1-6}alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said -$S(O)_nC_{1-6}$alkyl, -OR^6 or -NR^8R^9 groups ;

R is halo, C_{1-4}alkyl, C_{1-4}alkoxy, cyano, -$CONR^{10}R^{11}$, CO_2R^{12}, C_{1-4} alkyl$S(O)_n$, -NO_2, -NH_2, -$NHCOR^{13}$ or $SO_2NR^{14}R^{15}$ wherein n is 0, 1 or 2 and R^{10} to R^{15} are independently hydrogen or C_{1-4} alkyl ; and

is a ring of sub-formula (a) or (b) :



(a)

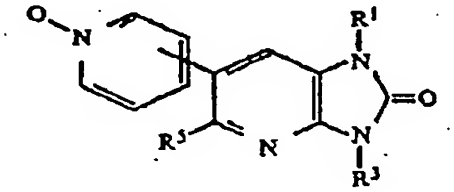


(b).

Preferred compounds include:

2-(5-cyano-2-propoxyphenyl)-7-methylthiopyrimido-[4,5-d]]pyrimidin-4(3H)-one,
2-(5-carboxamido-2-propoxyphenyl)-7-methylthiopyrimido[4,5-d]pyrimido-4(3H)-one, or
2-(5-carboxamido-2-propoxyphenyl)-7-cyclopropylamino[4,5-d]pyrimido-4(3H)-one,
or a pharmaceutically acceptable salt thereof.

U.S. Patent No. 5,010,086 discloses compounds of the formula

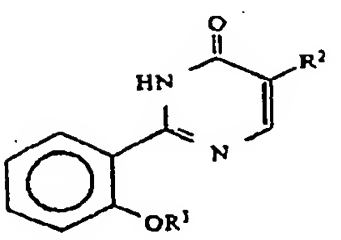


wherein
R_1 and R_3 are hydrogen or lower-alkyl;
R_5 is lower-alkyl or fluorinated lower-alkyl; and the pyridine-N-oxide is attached at the 4- or 3-position; or a pharmaceutically acceptable acid-addition salt thereof.

Preferred compounds include:

1,3-Dihydro-6-(4-pyridinyl)-5-trifluoromethyl-2H-imidazo[4,5-b]pyridin-2-one N-(py)-oxide

U.S. Patent No. 5,290,933 discloses compounds of the formula



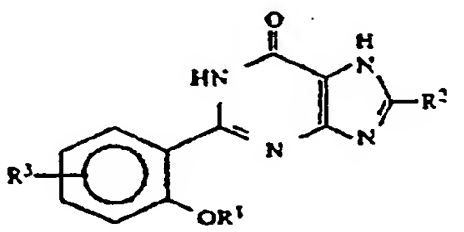
(1)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, phenylC_{1-6}alkyl or C_{1-6}alkyl substituted by 1 to 6 fluoro groups; and
R^2 is hydrogen, —NHCOR^3, or —CONR^{4}R^5, wherein R^3 is C_{1-6}alkyl, R^4 is C_{1-6}alkyl and R^5 is hydrogen or C_{1-6}alkyl.

Preferred compounds include:

N-methyl 1,6-dihydro-6-oxo-2-(2-propoxypnenyl)-pyrimidine-5-carboxamide,
N,N-dimethyl 1,6-dihydro-6-oxo-2-(2-propoxyphenyl)-pyrimidine-5-carboxamide,
5-acetamido-2-(2-propoxyphenyl)pyrimidin-4(3H)-one, or
2-(2-propoxyphenyl)pyrimidin-4(3H)-one,
or a pharmaceutically acceptable salt thereof.

U.S. Patent No. 5,073,559 discloses compounds of the formula



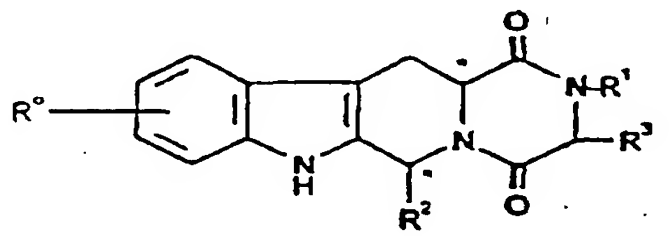
(1)

or pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-4}alkyl, phenylC_{1-4}alkyl or C_{1-4}alkyl substituted by 1 to 6 fluoro groups;
R^2 is hydrogen, hydroxy, C_{1-4}alkyl, phenyl, mercapto, C_{1-4}alkylthio, CF_3 or amino
R^3 is hydrogen, nitro, amino, C_{1-4}alkanoylamino, C_{1-4}-alkoxy, C_{1-4}alkyl, halo, $SO_2NR^4R^5$, $CONR^4R^5$, cyano or C_{1-4}alkyl$S(O)_n$;
R^4 and R^5 are independently hydrogen or C_{1-4}alkyl; and
n is 0, 1 or 2;
provided that R^3 is not hydrogen when R^1 is C_{1-6}alkyl or C_{2-6}alkenyl and R^2 is hydrogen or hydroxy.

Preferred compounds include:

2-(2 2-[2,2,2-trifluoroethoxy]phenyl)purin-6-one,
2-(2 2-cyclopropylmethoxyphenyl)purin-6-one,
2-(2 2-benzyloxyphenyl)purin-6,8-dione,
2-(2 2-propoxyphenyl)-8-trifluoromethylpurin-6-one,
2-(2 2-propoxyphenyl)-8-phenylpurin-6-one,
2-(2 2-propoxyphenyl)-8-methylpurin-6-one,
2-(2-propoxyphenyl)-8-mercaptopurin-6-one,
2-(2 2-propoxyphenyl)-8-methylthiopurin-6-one,
2-(2 2-propoxyphenyl)-8-aminopurin-6-one,
2-(2 2-propoxy-5-nitrophenyl)purin-6-one,
2-(2 2-propoxy-5-aminophenyl)purin-6-one,
2-(2-(2-propoxy-5-acetamidophenyl)purin-6-one,
2-(2 2-propoxy-4-methoxyphenyl)purin-6-one,
2-(2 2-propoxy-5-methoxyphenyl)purin-6-one,
2-(2 2-propoxy-4-methylphenyl)purin-6-one,
2-(2 2-propoxy-5-fluorophenyl)purin-6-one,
2-(2 2-propoxy-5-dimethylsulphamoylphenyl)purin-6-one,
2-(2 2-propoxy-5-methylsulphamoylphenyl)purin-6-one,
2-(2 2-propoxy-5-sulphamoylphenyl)purin-6-one,
2-(2 2-propoxy-4-methylthiophenyl)purin-6-one,
2-(2 2-propoxy-5-cyanophenyl)purin-6-one, and
2-(2-(2-propoxy-5-carbamoylphenyl)purin-6-one,
or a pharmaceutically acceptable salt thereof.

International Patent Publication PCT/EP96/03024 (WO97/03675) discloses compounds of the formula:

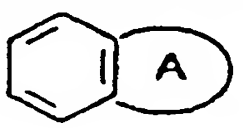


(I)

and salts and solvates (e.g. hydrates) thereof, in which:

R^0 represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring 

attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain.

Preferred compounds include:

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;
(6R, 12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2', 1' : 6,1] pyrido [3,4-b] indole-1,4-dione;
(5aR, 12R, 14aS)-1,2,3,5,6,11,12,14a-Octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo[1",2" : 4',5']pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-5-1,4-dione;
Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(3S, 6R,12aR)-2,3,6,7,12,12a-hexahydro-3-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;

and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

The specific compounds of the invention are:

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione (Compound A); and

(3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-1,4-dione (Compound B);

and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

Examples of cGMP PDE inhibitors contemplated in this invention are also described in United States Patent No. 5,346,901 and published International Patent Publication WO 94/28902, both of which documents are incorporated herein by reference.

Sildenafil, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-piperazine, and salts thereof are disclosed in WO 94/28902.

Phentolamine, 3-[[(4,5-dihydro-1H-imidazol-2-yl)methyl](4-methylphenyl)amino]phenol, and salts and esters thereof, and the use of phentolamine in the treatment of sexual dysfunction is disclosed in United States Patent No. 5,731,339, also incorporated herein by reference.

Sildenafil and phentolamine are each known to treat sexual dysfunction. The effectiveness of phentolamine for treatment of sexual dysfunction is demonstrated by test procedures described in U.S 5,731,339. Similar procedures can be used to determine the effectiveness of sildenafil and combinations of phentolamine and sildenafil.

Since the present invention relates to a method of treatment comprising the administration of a combination of two components, the components can be co-administered simultaneously or sequentially. Alternatively, a single pharmaceutical composition comprising sildenafil, or a pharmaceutically acceptable salt thereof, and phentolamine, or a

pharmaceutically acceptable salt or ester thereof, in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional oral dosage form such as a capsule, tablet, chewable tablets, powder, cachet, suspension or solution. The formulations can be prepared using conventional pharmaceutical excipients and additives using conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

Information on formulations comprising sildenafil are disclosed in WO 94/28902. Representative formulations comprising phentolamine are disclosed in U.S. 5,731,339. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms as disclosed in the aforementioned patent or application may readily be modified using the knowledge of one skilled in the art.

A typical formulation for sildenafil comprises 25, 50 or 100 mg of active and as inactive ingredients, microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hydroxypropylmethylcellulose, titanium dioxide, lactose, triacetin, and FD&C Blue #2 aluminum lake.

A typical formulation for phentolamine is as follows:

Component	mg/Tablet (w/w%)
phentolamine mesylate, USP	40 (10)
Microcrystalline Cellulose, NF	341.6 (85.4)
Croscarmellose Sodium, NF	16 (4.0)
Colloidal Silicon Dioxide, NF	0.4 (0.1)
Magnesium Stearate, NF	2 (0.5)
Total	400 (100)

The following are exemplary formulations for the phentolamine mesylate/sildenafil citrate combination:

Direct Compression Formulation

Component	mg/Tablet
Phentolamine Mesylate	80
Sildenafil Citrate	100
Microcrystalline Cellulose	207.5-209.0
Croscarmellose Sodium	10
Silicon Dioxide	0.5
Magnesium Stearate	0.5-2
Total	400

The direct -compression formulation is manufactured by blending the active ingredients and excipients and compressing the mixture into tablets.

Wet-Granulation Formulation

Component	mg/Tablet
Phentolamine Mesylate	80
Sildenafil Citrate	100
Microcrystalline Cellulose	80
Lactose	114-115.5
Sodium Starch Glycolate	12
Povidone	12
Water	(evaporates)
Magnesium Stearate	0.5-2
Total	400

The wet-granulation formulation is manufactured using the following steps:

1. the active ingredients are combined with microcrystalline cellulose, lactose and sodium starch glycolate in a mixer/granulator;
2. povidone is added to water to form a solution;
3. the granulating solution (from step 2) is added to the powder blend (from step 1) with agitation to form a granulation, and the resulting granulation is dried;
4. the dry granulation is blended with magnesium stearate; and

5. the mixture is compressed into tablets.

Fast-Dissolving Formulations

A

Component	mg/Tablet
Phentolamine Mesylate	40
Sildenafil Citrate	50
Gelatin	30
Mannitol	29
Flavor	1
Water	(evaporates)
Total Dry Tablet Weight	150

The above tablet form is manufactured by:

1. forming a uniform dispersion achieved by adding the active ingredients and excipients to water with agitation;
2. filling aliquots of the dispersion into molds; and
3. lyophilizing to form dry tablets.

B

Component	mg/Tablet
Phentolamine Mesylate	40
Sildenafil Citrate	50
Microcrystalline Cellulose	95
Crospovidone	10
Sodium Bicarbonate	2
Citric Acid	2
Flavor	1
Total	200

The tablets are made by blending the combination of the actives and excipients and compressing the mixture into tablets.

The compounds in the combination of this invention for treating sexual dysfunction are administered in accordance with the treatment regimens described in each of the above listed publications. For example, for a combination of a Type V cGMP PDE inhibitors such as

Sildenafil in combination with phentolamine, the typical dosage is 5 to 100 mg of Sildenafil and 5 to 75 mg of phentolamine per dose, usually administered approximately one hour prior to intercourse. It is expected that the dosage of the individual components in the combination will be less than the dosage required when the individual components are administered alone. The exact dose of either component of the combination to be administered and the timing thereof is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient. Where the components of a combination are administered separately, the separate dosage forms need not be administered simultaneously.

Since the present invention relates to treatment with a combination of active ingredients wherein said active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit is contemplated wherein two separate units are combined: for example, a sildenafil pharmaceutical composition and a phentolamine pharmaceutical composition. The kit will preferably include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. tablet and capsule) or are administered at different dosage intervals.

What is claimed is:

1. A pharmaceutical composition for the treatment of human sexual dysfunction comprising a therapeutically effective amount of phentolamine or a pharmaceutically acceptable salt or solvate or ester thereof, a therapeutically effective amount of a cGMP PDE V inhibitor or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

2. A composition of claim 1 wherein the cGMP PDE V inhibitor is sildenafil or a pharmaceutically acceptable salt or solvate thereof.

3. The composition of claim 1 wherein the phentolamine is phentolamine mesylate.

4. The composition of claim 1 wherein the sildenafil is sildenafil citrate.

5. The composition of claim 1 wherein the phentolamine is phentolamine mesylate and the cGMP PDE V inhibitor is sildenafil citrate.

6. A method of treating human sexual dysfunction comprising the simultaneous or sequential administration of a therapeutically effective amount of phentolamine or a pharmaceutically acceptable salt, solvate or ester thereof, and a therapeutically effective amount of a cGMP PDE V inhibitor or a pharmaceutically acceptable salt thereof.

7. The method of claim 6 wherein the cGMP PDE V inhibitor is sildenafil or a pharmaceutically acceptable salt or solvate thereof.

8. The method of claim 6 wherein the phentolamine is phentolamine mesylate.

9. The method of claim 6 wherein the cGMP PDE V inhibitor is sildenafil citrate.

10. The method of claim 6 wherein the phentolamine is phentolamine mesylate and the cGMP PDE inhibitor V is sildenafil citrate.

11. A kit comprising in separate containers in a single package, pharmaceutical compositions for use in combination to treat sexual dysfunction which comprises in one container a therapeutically effective amount phentolamine or a pharmaceutically acceptable salt, solvate or ester thereof in a pharmaceutically acceptable carrier and in a second container a therapeutically effective amount of a cGMP PDE V inhibitor or a pharmaceutically acceptable salt of solvate thereof in a pharmaceutically acceptable carrier.

12. A pharmaceutical composition for the treatment of human sexual dysfunction comprising a therapeutically effective amount of a first vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof, a therapeutically effective amount of a second vasodilating agent or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition of claim 12 wherein said first vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof is an adrenergic blocker.

14. The pharmaceutical composition of claim 13 wherein said adrenergic blocker is an alpha-adrenergic blocker.

15. The pharmaceutical composition of claim 14 wherein alpha adrenergic blocker is selected from the group consisting of an alpha1-adrenergic blocker, an alpha2-adrenergic blocker or both an alpha1-adrenergic blocker and an alpha2-adrenergic blocker.

16. The pharmaceutical composition of claim 12 wherein said second vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof is a cGMP PDE inhibitor.

17. The pharmaceutical composition of claim 12 wherein said first vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof is an adrenergic blocker and said second vasodilating agent

or a pharmaceutically acceptable salt or solvate or ester thereof is a cGMP PDE inhibitor.

18. The pharmaceutical composition of claim 17 wherein the adrenergic blocker is selected from the group consisting of phentolamine, phentolamine mesylate, phentolamine hydrochloride, phenoxybenazmine, tolazoline, dibenamine, yohimbine, terazosin, doxazosin and prazosin.

19. The pharmaceutical composition of claim 17 wherein the cGMP PDE inhibitor is a cGMP PDE V inhibitor.

20. The pharmaceutical composition of claim 17 wherein the cGMP PDE V inhibitor is selected from the group consisting of: sildenafil,
(6R, 12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrizino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (Compound A), and
(3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (Compound B) or a pharmaceutically acceptable salt or solvate thereof.

21. A method of treating human sexual dysfunction comprising the simultaneous or sequential administration of a therapeutically effective amount of a therapeutically effective amount of a first vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof, a therapeutically effective amount of a second vasodilating agent or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/07046

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/415 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GOMAA A ET AL: "Topical treatment of erectile dysfunction: randomised double blind placebo controlled trial of cream containing aminophylline, isosorbide dinitrate, and co-dergocrine mesylate 'see comments!." BMJ (CLINICAL RESEARCH ED.), (1996 JUN 15) 312 (7045) 1512-5. , XP002115285 abstract the whole document ---	12-15,21
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 September 1999	28/09/1999

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 99/07046

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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